New Strategy for Synthesis of Fluorinated Organic Compounds

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Introduction

1.1. Fluorinated compounds in life

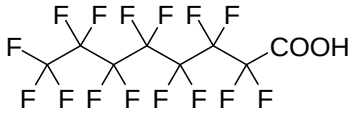
Fluorinated compounds are used in many drugs, agrochemicals, and tools such as home electronics and analytical instruments that are used in daily life. For example, “mouthwash liquid” used for the prevention of tooth decay and Teflon frying pans, which are used in cooking to prevent the food from burning easily, are familiar objects. Moreover, AlF_3 is used as an additive in the electrolytic refining of aluminum; SF_6 is used for the dry etching of insulators, semiconductor products, and liquid crystal panels. Furthermore, HF and F_2 are used to enrich uranium by transforming uranium oxide into low-boiling uranium hexafluoride (UF_6, boiling point 57 °C). Thus, fluorinated compounds are indispensable in our lives. Most natural sources of fluorine are remarkably stable minerals such as fluorite (CaF_2) and ice stone (Na_3AlF_6); however, they are difficult to use as fluorine source directly. Therefore, they are transformed into other fluorine compounds with high chemical reactivity, e.g., fluorite is treated with concentrated hydrochloric acid to produce HF and is the most commercially available fluorine source. Most fluorinated organic compounds are derived by chemical synthesis. Next, the characteristics and methods of preparation of fluorinated organic compounds are described.[1]

1.2. The feature of fluorinated organic compounds

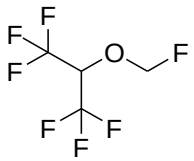
Fluorinated organic compounds are divided into “perfluorinated compounds” and “partially fluorinated compounds” as described below.

1.2.1. Perfluorinated compounds

Perfluorinated compounds are organic compounds in which all or most hydrogen (H) atoms are replaced by fluorine (F) atoms. They have high bonding energies, low polarizabilities decreasing induced dipole express surface, spectrophotometric, and electrical characteristics. These compounds are widely used as functional materials in electrical, chemical, medical, and other industries (Figure 1).



PFOA: surface preparation agent



Sevoflurane: anesthesia

Figure 1. Perfluorinated compounds

(Characteristics)

1) Resistance properties

excellent heat resistance, remarkable chemical resistance, weather resistance, inflammation, and other physical traits

2) Surface characteristics

non-adhesive, water/oil repellency, scratch proof, and low frictional coefficient

3) Light characteristics

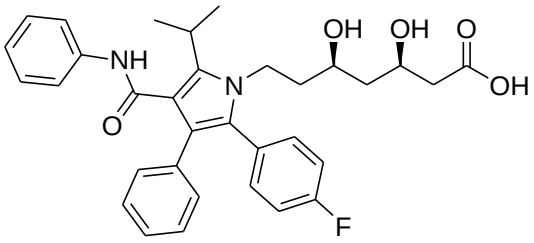
low refractive indices and high opaqueness

4) Electrical characteristics

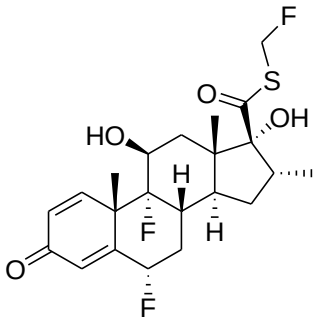
highly insulating, low electric inductance, and small dielectric loss

1.2.2. Partially fluorinated compounds

Partially fluorinated compounds are organic compounds in which some of the H atom(s) is(are) substituted by F atom(s). The substitution(s) render(s) various effects, such as increasing polarity, mimicking biological systems, blocking metabolism, and increasing hydrophobicity. These compounds are mainly used in medical and agrochemical fields.



Atorvastatin: dyslipidemia, cardiovascular disease



Fluticasone: anti-inflammatory

Figure 2. Partially fluorinated compounds

(Characteristics)

1) Polarity effect

The high electronegativity of the fluorine atom (Figure 3) decreases the electron density of the carbon atom attached to it and surrounding atoms, thus preventing electrophilic attacks such as enzyme oxidation, resulting in enhanced pharmacological

effect, reduced side effects, and new bioactivity.

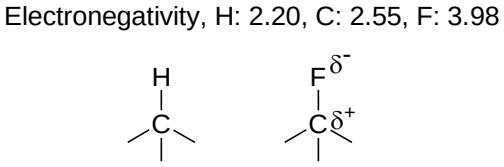


Figure 3. Polarized C–F bond

2) Mimic effect

A fluorine atom is quite small in size, being only slightly larger than a hydrogen atom (van der Waals radius, F: 1.35Å, H: 1.10Å). Thus, it is expected that a biologically active agent, in which a particular H atom is replaced by a fluorine atom, would circumvent the block in stereognostic recognition because of its polarity effect during *in vivo* absorption.

3) Blocking effect

The C–F bond is more stable than C–H, C–Cl, and other bonds (Table 1); therefore, it is stable towards substitution, reduction, and oxidation reactions by enzymes *in vivo*. Therefore, metabolic degradation of the site around the C–F bond is suppressed.

Table 1. Bond energies and bond lengths

C–X bond	C–F	C–H	C–Cl	C–Br	C–I
Bond energy (kJ/mol)	485	411	327	285	213
Bond lengths (pm)	135	109	177	194	214

4) Increase hydrophobicity effect

Fluorine atoms increase the lipophilicity of the compound and promote assimilation

and transportation *in vivo;* in particular, trifluoromethyl or perfluoroalkyl-substituted compounds exhibit higher lipophilicity than the precursors.

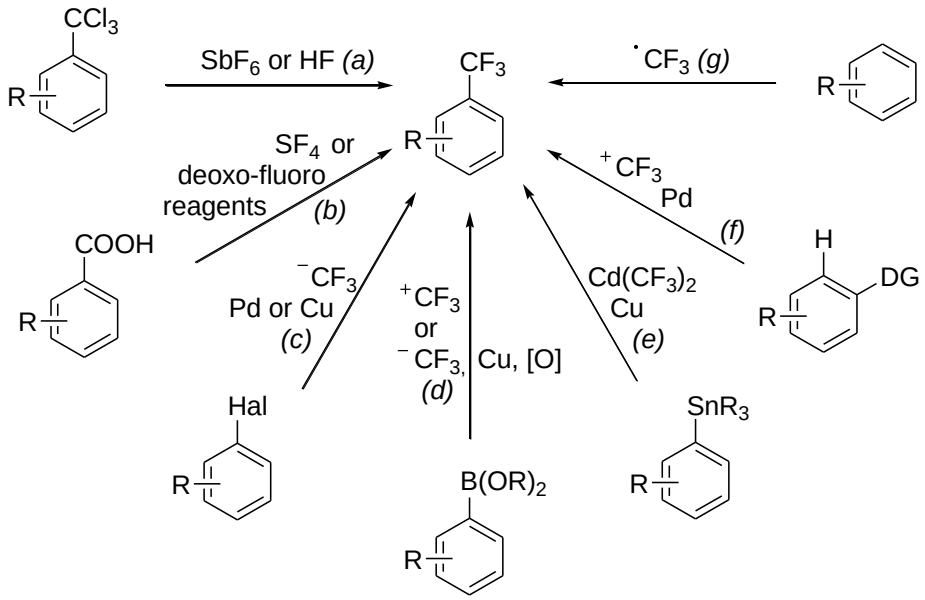
1.3. Introduction of fluorine and fluorinated functional groups

The degree of fluorination is difficult to control in reactions using F_2 or HF because most simple fluorine sources are useful for introducing large amounts of fluorine atoms; therefore, most simple fluorine sources are ineffective for the preparation of partially fluorinated compounds. Moreover, these methods need specialized equipment and techniques because of toxicity and causticity; therefore, synthesis methods using HF or F_2 are ineffective in the preparation of partially fluorinated compounds. Therefore, diverse methods have been developed for introducing fluorine and fluorine-containing functional groups at specific positions in organic compounds.[2]

1.3.1. Introduction of trifluoromethyl and perfluoroalkyl groups

Diverse trifluoromethylated arenes can be prepared by converting various functional groups to the trifluoromethyl group (Scheme 1).[3] In addition to the classical methods, toxic SF_4 is used to convert a trihalomethyl group to the corresponding trifluoromethyl group (Reaction type *a*).[3a–c] New Deoxo-Fluor reagents have been developed for the conversion of a carboxylic acid group to the corresponding trifluoromethyl group (Reaction type *b*).[3d–g] In particular, the studies on cross-coupling reactions using trifluoromethylating reagents derived from various chemical species ($^{+}CF_3$, $^{-}CF_3$, $^{\bullet}CF_3$) with functional groups (halogen, $B(OR)_3$, SnR_3, H etc.) on arene have been increasing

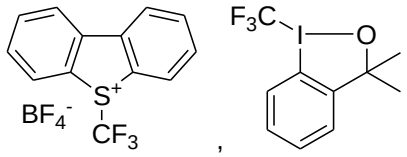
over the past decade (Reaction type *c*–*g*).[3h–p]



sources of $^{-}CF_3$

Et_3SiCF_3, FSO_2CF_2COOMe, CF_3CO_2Na
$K[CF_3B(OMe)_3]$, CF_3H, CF_3Cu, etc.

sources of $^{+}CF_3$



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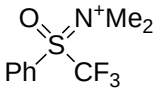
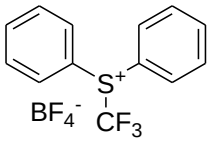


BF_4^- , CF_3I, etc.

sources of $^{\bullet}CF_3$



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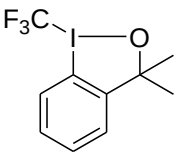
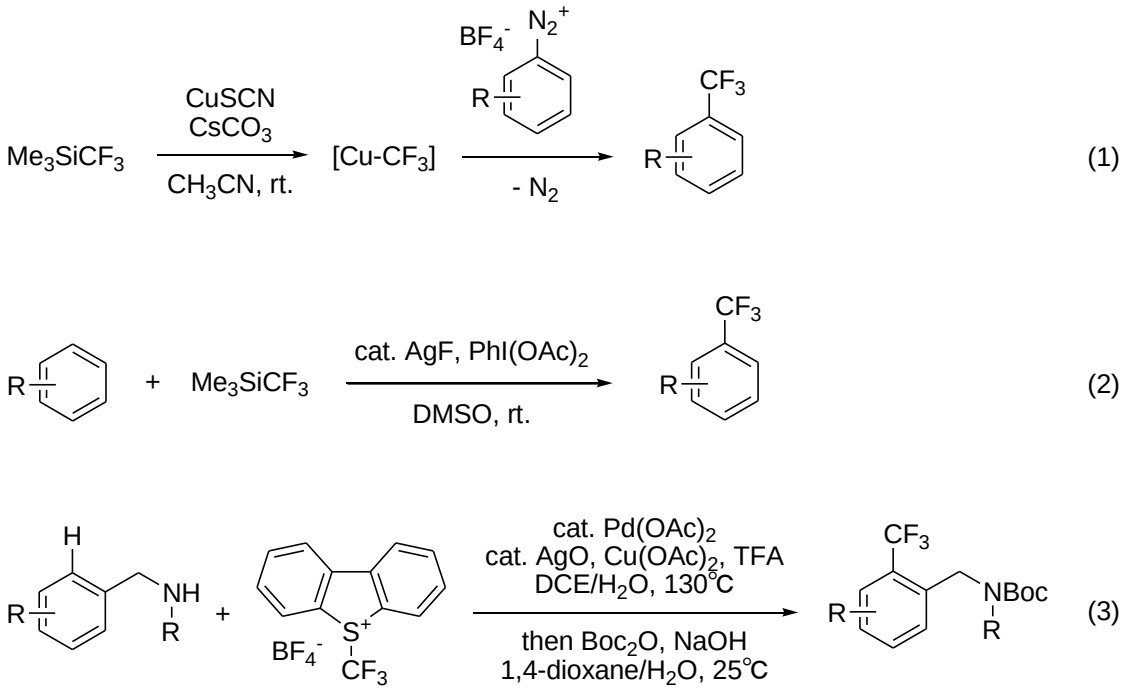


,
CF_3SO_2Cl, CF_3I, $(CF_3SO_2)_2Zn$
CF_3SO_2Na, Me_3SiCF_3, etc.

Scheme 1. Strategy for the introduction of trifluoromethyl groups

Scheme 2 shows the examples of recently published aryl trifluoromethylation methods.[4] Gooβen and co-workers reported the Sandmeyer trifluoromethylation of arenediazonium tetrafluoroborates. The diazonium salt is added to a Cu–CF_3 species

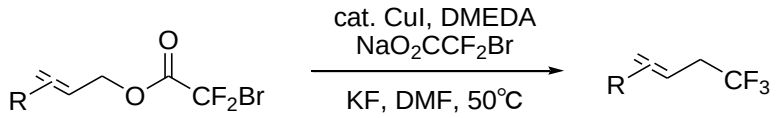
preformed from CuSCN and Me_3SiCF_3 in the presence of Cs_2CO_3; this method allows the straightforward synthesis of trifluoromethylated arenes from the corresponding aromatic amines (equation 1).[4a] The Greney group reported silver-catalyzed trifluoromethylation under mild conditions at room temperature in which the trifluoromethyl radical species ($^{\bullet}CF_3$), generated by the reaction of Me_3SiCF_3 with $PhI(OAc)_2$ and AgF, reacts with arenes (equation 2).[4b] The Yu group reported the Pd-catalyzed *ortho*-C–H trifluoromethylation of benzylamines, in which additives, such as H_2O and Ag_2O, were found to be crucial for obtaining good yields (equation 3).[4c]



Scheme 2. Recently reported aryl trifluoromethylation

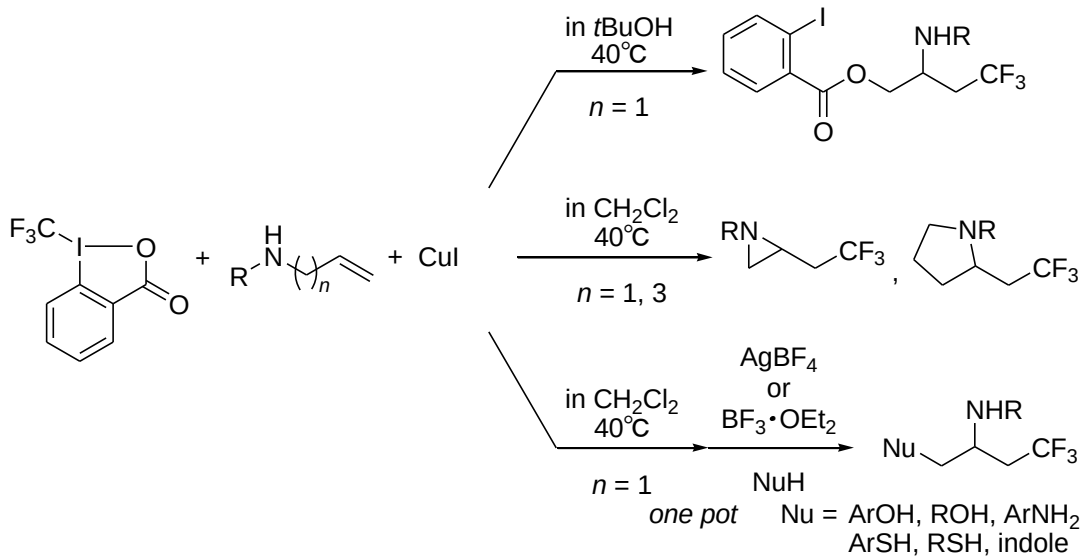
The introduction of a trifluoromethyl group to an sp^3-carbon atom, such as an allylic position, is also an area of active research.[5] Recently, the Altman group reported

unique allylic trifluoromethylation from allyl bromodifluoroacetates. This reaction proposes Cu–CF_3, generated from the CuI/NaO_2CCF_2Br/KF system, as the active species in the reaction (Scheme 3).[5a]



Scheme 3. Recently reported allylic trifluoromethylation

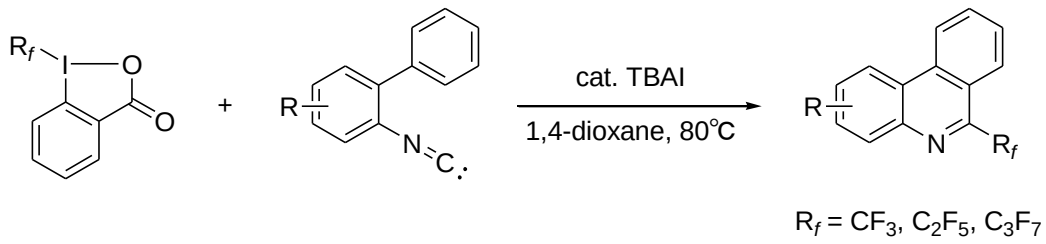
Not only the conversion of different functional groups to trifluoromethyl groups, but also the transformation of different structures has attracted interest.[6] Recently, the Sodeoka group reported *N*-migratory oxy- and amino-trifluoromethylation of allylamine derivatives using the Cu(I)/Togni reagent system (Scheme 4).[6a]



Scheme 4. Synthesis of β-trifluoromethyl amines

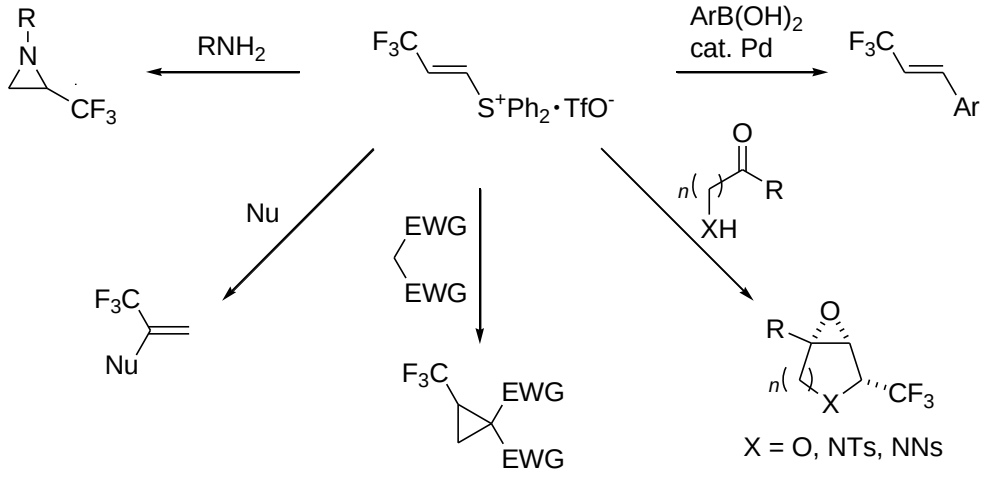
On the other hand, the Studer group reported the synthesis of 6-trifluoromethylated

phenanthridines starting from readily prepared isonitriles, in the absence of a transition metal catalyst. In addition, this method can also be applied to the synthesis of perfluoroalkylated phenanthridines (Scheme 5).[6b]



Scheme 5. Synthesis of β-trifluoromethyl amines

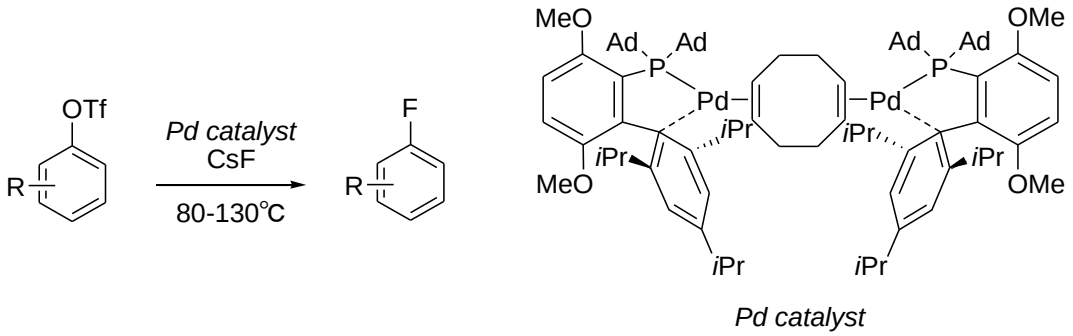
Chemical building blocks are effective for the synthesis of trifluoromethylated compounds,[7] e.g., β-CF_3-vinylsulfonium salt recently developed by our group is useful to introduce a trifluoromethyl group in three-carbon homologation reactions (Scheme 6).[7a–e]



Scheme 6. Applications of β-CF_3-vinylsulfonium salt

1.3.1. Introduction of a fluorine atom

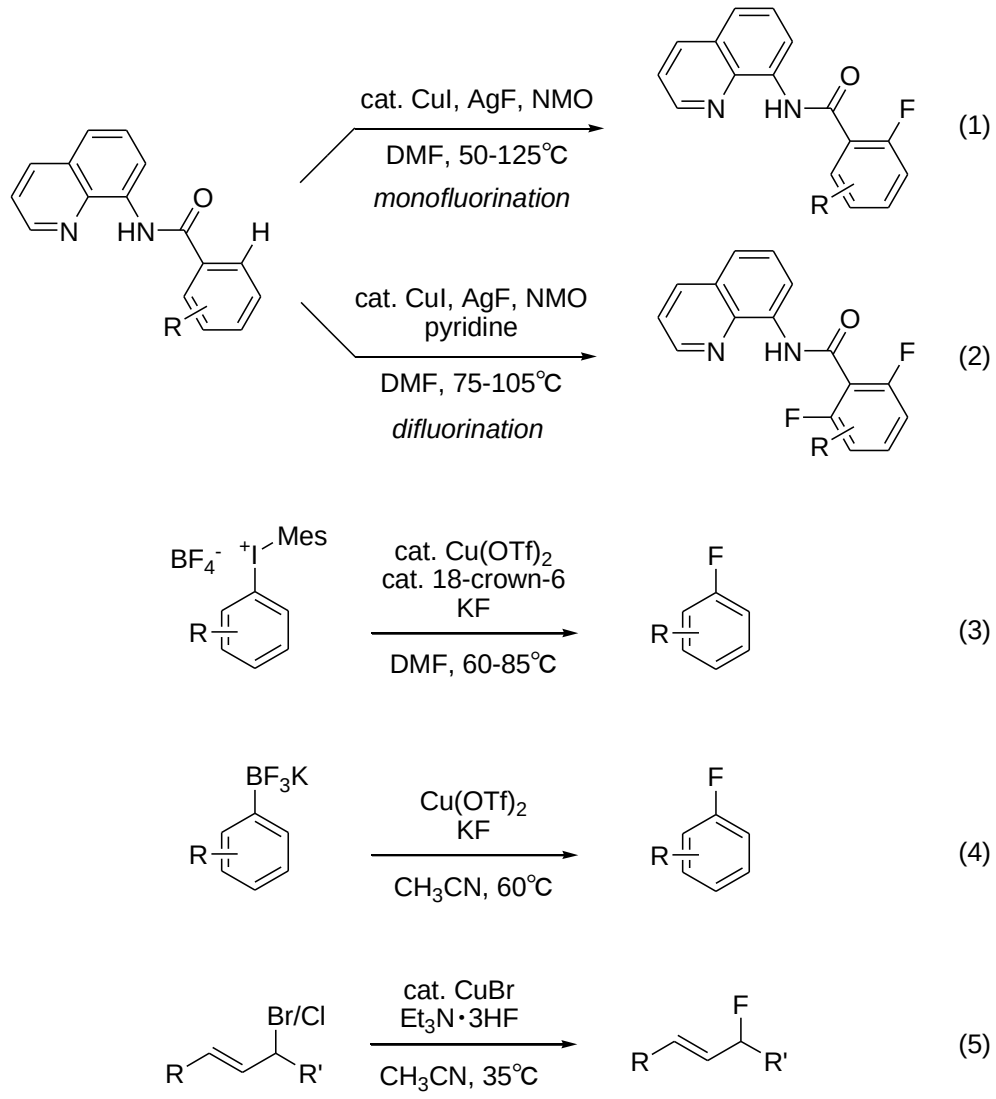
In the recent years, traditional metal-catalyzed fluorination reactions have been actively studied, particularly the reductive elimination of Ar-[M]-F species for aryl fluorination has been proven to occur through Pd(0)/Pd(II), Pd(II)/Pd(IV), or Cu(I)/Cu(III) catalytic cycles.[8] Recently, the Buchwald group reported the Pd-catalyzed fluorination of aryl triflates. They developed a new Pd catalyst based on a bulky biaryl phosphine ligand that allows the introduction of fluorine atoms into the triflate derivatives of various naturally occurring phenols (Scheme 7).[8a]



Scheme 7. Pd-catalyzed fluorination of aryl triflates

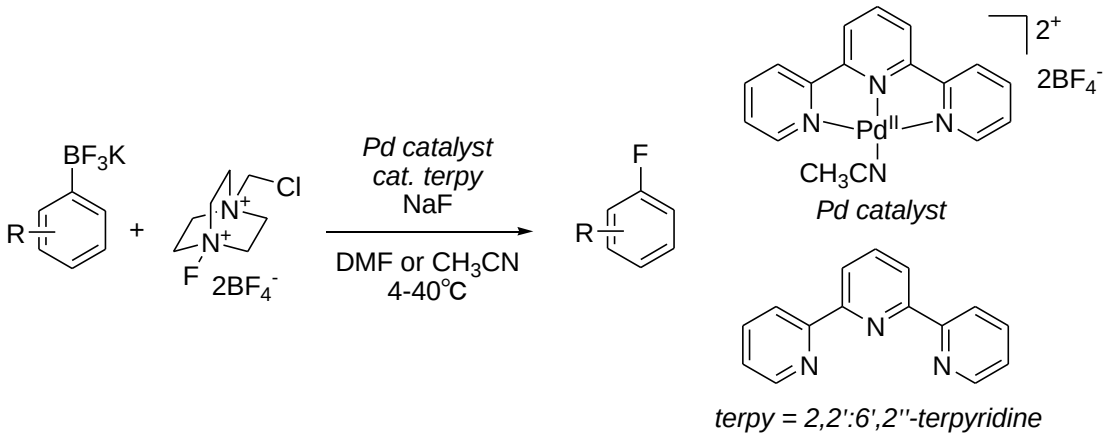
On the other hand, new Cu-catalyzed nucleophilic fluorinations have been recently reported (Scheme 8).[8b–e] The Daugulis group reported the direct auxiliary-assisted fluorination of β-sp^2 C–H bonds of benzoic acid derivatives; selective mono- or difluorination could be achieved by simply changing the reaction conditions (equations 1, 2).[8b] The Sanford group reported the fluorination of unsymmetrical diaryliodonium salts with KF. They conduced density functional theory (DFT) calculations on the $Cu(OTf)_2$ catalyzed fluorination of $[Ph_2I]BF_4$ with F^- ions to establish the Cu(I)/Cu(II) catalytic cycle (equation 3).[8c] They also reported the fluorination of aryl

trifluoroborates with potassium fluoride, mediated by an excess amount of $Cu(OTf)_2$ (equation 4).[8d] The Liu group reported the Cu-catalyzed fluorination of allylic halides. This reaction allows the regioselective transformation of internal allylic bromides and chlorides to fluorine using $Et_3N{\cdot}3HF$ as the fluorine source. For the C–F bond formation step in this reaction, a mechanism was proposed involving both the direct reductive elimination of allyl-[Cu(III)]-F intermediate and S_N2-type nucleophilic attack of the allyl/Cu(III) complex from F^-, which could not be differentiated at this stage (equation 5).[8e]



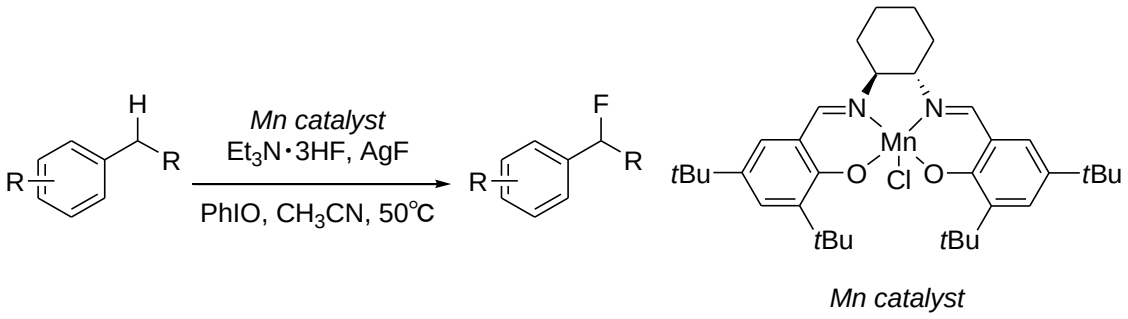
Scheme 8. Cu-catalyzed fluorination reactions

Recently, the Litter group reported Pd(III) catalyzed fluorination of arylboronic acid derivatives using Selectfluor as the fluorine source. They isolated and characterized the Pd(III) intermediate and proposed the single-electron transfer (SET) mechanism involving an unusual Pd(III) intermediate (Scheme 9).[9]



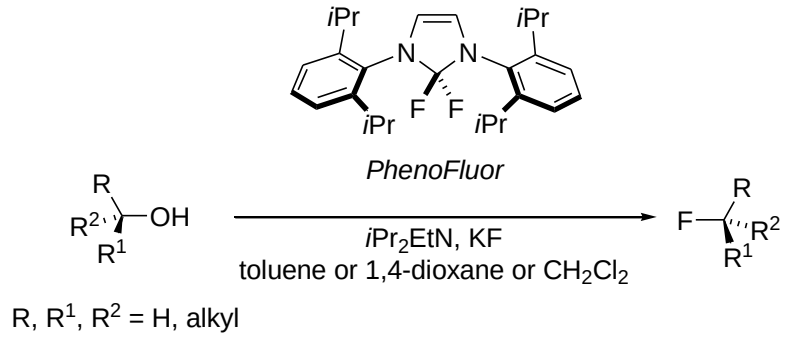
Scheme 9. Pd-catalyzed fluorination reactions

The Groves group reported the Mn-catalyzed benzylic C–H fluorination that allows the formation of benzylic fluorides directly from C–H bonds using simple and easily handled nucleophilic fluoride reagents, $Et_3N{\cdot}3HF$.[10]



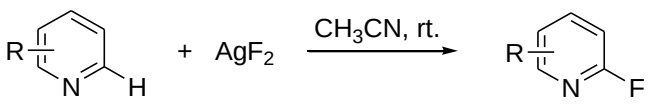
Scheme 10. Mn-catalyzed fluorination reactions

Deoxyfluorination is effective for introducing one or more fluorine atoms into organic compounds.[11] However, the current deoxyfluorination methods are commonly characterized by limited functional group tolerance, side reactions such as elimination, and instability or explosion of the reagents upon heating. Recently, the Ritter group reported the late-stage deoxyfluorination of alcohols using the Deoxo-Fluor reagent, PhenoFluor, to solve these problems. PhenoFluor is a crystalline, non-explosive solid, and is commercially available.[11a]



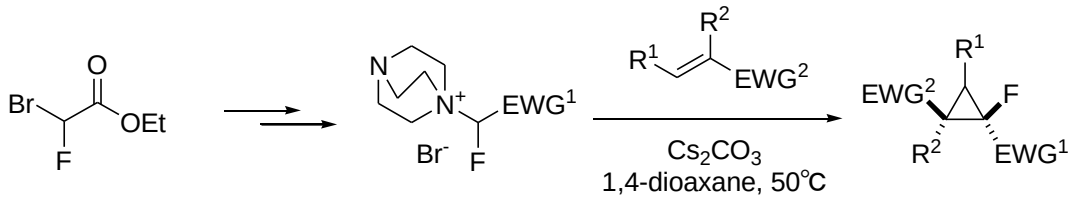
Scheme 11. Deoxyfluorination using PhenoFluor

The Hartwig group reported the fluorination of pyridines and diazine derivatives with AgF_2. This selective fluorination reaction allows the access to 2-fluoropyridines and related 2-fluoroazines, which are medicinally important compounds under mild reaction conditions (Scheme 12).[12]



Scheme 12. Regioselective fluorination of pyridines with AgF_2

Mono-fluorinated building blocks are usually effective for introducing fluorine to construct mono-fluorinated organic compounds.[13] Recently, the Jubalut group reported the diastereoselective access to functionalized mono-fluorinated cyclopropanes using mono-fluorinated quaternary ammonium salts derived from ethyl bromofluoroacetate.[13a]



Scheme 13. Mono-fluorinated cyclopropanation reaction

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Chapter two

Mizoroki-Heck Reaction of (1-Fluorovinyl)methyldiphenylsilane with Aryl Iodides

2.1. Introduction

Introduction of an aromatic ring to fluorinated olefins is an important task in organofluorine chemistry. It is well-accepted that the Mizoroki-Heck reaction has proven to be a useful method for the arylation of general olefins in organic synthesis.[1] A wide range of olefins containing various substituents can participate in the reaction,[2] however there are very few reports concerning the use of fluoroolefins.[3] In addition, the Mizoroki-Heck reaction of silylated olefins are considered to be difficult because of its tendency toward elimination of the silyl moiety instead of hydrogen.[4] To the best my knowledge, there exist no reports concerning the use of silylated fluoroolefins for this reaction. Recently, much effort has been performed to add the fluorine to organic molecules owing to its remarkable effects on their structure, stability, reactivity, and biological activity.[5] The stereoselective synthesis of fluoroolefins having a functional group also remains one of the challenging objectives. Our group have reported a facile synthesis of (1-fluorovinyl)methyldiphenylsilane and its application for the construction of a wide range of fluorovinyl compounds.[6,7] From alternative synthetic point of view, the silane should be a promising candidate for the Mizoroki-Heck reaction. The author describes here the first example of the Mizoroki-Heck reaction of silylated fluoroolefin

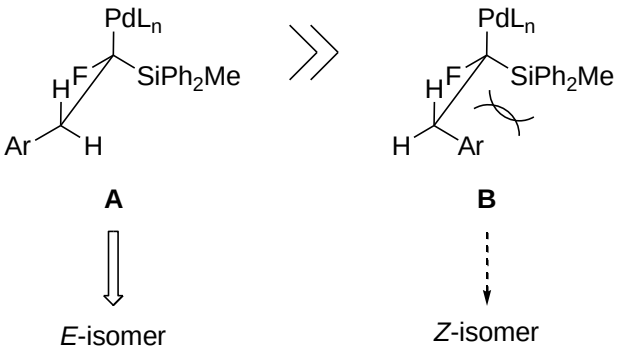
and a synthetic utilization of the resulting coupling products to transform the corresponding cis-β-fluorostyrene derivative.

2.2. Result and discussion

The author started to examine the Mizoroki-Heck reaction by using (1-fluorovinyl)methyldiphenylsilane **1** and 4'-iodoacetophenone **2a** as a model compound in order to explore the viability. The author found, in the early experiment, that the reaction gave the desired product **3a** albeit in 25 % yield and with low stereoselectivity (*E*/*Z* = 60/40) along with **1** and some byproduct in the presence of 10 mol % of $Pd(OAc)_2$ and Ag_2CO_3 (3 equiv.) in DMF at room temperature for 2 h.[8] In order for the complete consumption of the unreacted **1**, the longer reaction times caused **3a** to decompose and decrease the yield. The author also noticed that when the reaction was conducted at an elevated temperature (50 ℃), the reaction was complicated to afford none of **3a**. These hopeless observations forced me to continue examinations of a variety of reaction factors such as Palladium catalyst, a base, a solvent, temperature, and additives.

The author showed some results of the reaction conditions in Table 1. As seen to this Table 1, the author determined that the entry 13 was the optimal reaction conditions. The reaction proceeded to afford the desired product **3a** in 72 % yield with excellent stereoselectivity (*E*/*Z* = 98/2). The *E*/*Z* stereochemistry of the product **3a** was assigned on the basis of the coupling constant of its ^{1}H and ^{19}F NMR. The *J* value of 50.3 Hz between the fluorine atom and vinyl proton supported the corresponding

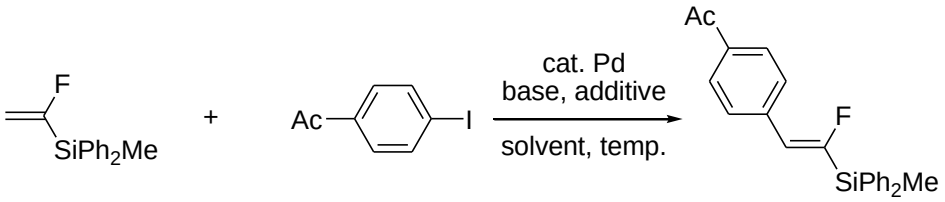
E-configuration. The embedded aryl group is located at the trans position toward the bulky methyldiphenylsilyl group. This trans relationship between the aryl and the silyl group is similar to that of the aryl and acyl groups in the Mizoroki-Heck reaction using 3-fluoro-3-buten-2-one.[3d] The plausible reaction mechanism for the excellent *E*-stereoselectivity should be ascribed to the contribution of the stable conformer **A** prior to the required *syn* elimination (Scheme 1).



Scheme 1. Stability of palladium intermediates

It is noteworthy that the reaction system containing $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (3 equiv.) in dioxane at 90 ℃ was essential for the successful reaction. Except for these conditions, none of other combinations using other bases, Pd sources, and different solvents failed to improve the yield (entries 2–10). When the author conducted the reaction in the presence of the lower loading of Ag_2CO_3 (1–2 equiv.) and $Pd(OAc)_2$ (5 mol %), the lower yields (entries14–16) were observed. Although the use of MS4Å plays an important role in this reaction, its contribution is not clear at present. The author guessed that it might remove a trace amount of water probably generated from decomposition of H_2CO_3 resulted from Ag_2CO_3 in the reaction mixture.

Table 1. Optimization of reaction conditions for the Mizoroki-Heck reaction of **1**[a]



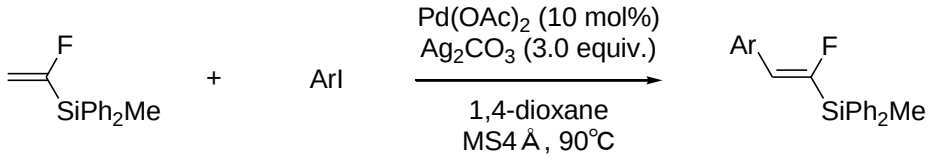
1 **2a** **3a**

entry	Pd (10 mol %)	base (equiv.)	solvent	temp. (℃)	time (h)	additive	yield[b] (%)	*E*/*Z*[c]
1	$Pd(OAc)_2$	Ag_2CO_3 (3)	DMF	rt	2	none	25	60/40
2	$Pd(OAc)_2$	NaOAc (3)	DMF	50	12	none	trace	-
3	$Pd(OAc)_2$	TEA (3)	DMF	100	12	none	0	-
4	$PdCl_2$	Ag_2CO_3 (3)	DMF	50	10	none	0	-
5	$Pd(PPh3)_4$	Ag_2CO_3 (3)	DMF	50	12	none	0	-
6	$Pd(OAc)_2$	Ag_2CO_3 (3)	DMSO	100	12	none	0	-
7	$Pd(OAc)_2$	Ag_2CO_3 (3)	NMP	100	12	none	0	-
8	$Pd(OAc)_2$	Ag_2CO_3 (3)	DMI	100	10	none	0	-
9	$Pd(OAc)_2$	Ag_2CO_3 (3)	MeCN	50	12	none	0	-
10	$Pd(OAc)_2$	Ag_2CO_3 (3)	THF	60	12	none	0	-
11	$Pd(OAc)_2$	Ag_2CO_3 (3)	dioxane	90	12	none	40	98/2
12	$Pd(OAc)_2$	Ag_2CO_3 (4)	dioxane	90	10	MS4Å	72	98/2
13	$Pd(OAc)_2$	Ag_2CO_3 (3)	dioxane	90	12	MS4Å	72	98/2
14	$Pd(OAc)_2$	Ag_2CO_3 (2)	dioxane	90	12	MS4Å	62	98/2
15	$Pd(OAc)_2$	Ag_2CO_3 (1)	dioxane	90	12	MS4Å	48	98/2
16	$Pd(OAc)_2$[d]	Ag_2CO_3 (3)	dioxane	90	20	MS4Å	60	97/3
17	$Pd(OAc)_2$	Ag_2CO_3 (3)	dioxane	70	10	MS4Å	56	99/1

[a] The reaction of **1** (1.0 equiv.) with **2** (2.0 equiv.) was carried out. [b] Isolated yield. [c] Determined by GC-MS. [d] $Pd(OAc)_2$ (5 mol %) was used.

With the optimized reaction conditions in hand, the author examined the substrate scope. The results are shown in Table 2. The substrate scope was wide and the position of the aromatic ring as well as the nature of the substituents did not essentially affect the reaction. The chemical yield of the reaction was generally good to high. The author found that the stereoselectivity of the reaction was excellent except for **3d**.[9] A wide range of functional groups such as alkyls, esters, ethers, a nitro, a cyano, and halogens were tolerated (entries 1–14). Unfortunately, no heteroaryl iodides such as 2-iodothiophene and 2-iodopyridine participated in the reaction (entries 15, 16). In addition, 4'-bromoacetophenone as a more available and less expensive aryl bromide was found to be unsuitable for the reaction (entry 17). In these cases, no reactions occurred and both of the starting materials were almost recovered intact.

Table 2. Substrate scope of aryl iodides[a]

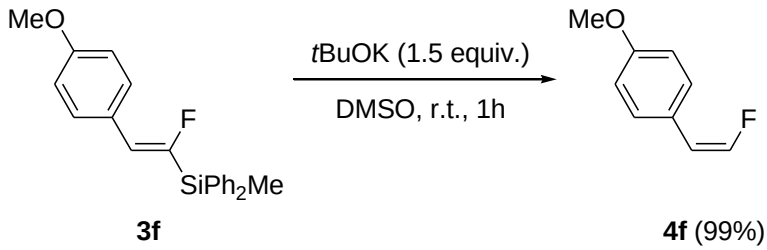


1 **2** **3**

entry	ArI	**3**	time (h)	yield[b] (%)	*E*/*Z*[c]
1	4-AcC_6H_4I	**3a**	4	72	98/2
2	4-$EtO(=O)C_6H_4I$	**3b**	2	63	99/1
3	4-$O_2NC_6H_4I$	**3c**	4	81	96/4
4	4-NCC_6H_4I	**3d**	3	63	93/7
5	4-$CF_3C_6H_4I$	**3e**	5	77	97/3
6	4-$MeOC_6H_4I$	**3f**	5	61	97/3
7	2-FC_6H_4I	**3g**	19	70	98/2
8	2-ClC_6H_4I	**3h**	4	88	97/3
9	2-BrC_6H_4I	**3i**	3	85	98/2
10	2-$MeO(=O)C_6H_4I$	**3j**	2	60	98/2
11	2-EtC_6H_4I	**3k**	6	65	98/2
12	3-$MeOC_6H_4I$	**3l**	4	78	97/3
13	2,4-MeC_6H_4I	**3m**	18	67	98/2
14	C_6H_4I	**3n**	6	72	96/4
15	thiophene-2-I	**3o**	24	NR[d]	-
16	pyridine-2-I	**3p**	24	NR[d]	-
17	4-AcC_6H_4Br[e]	**3q**	24	NR[d]	-

[a] The reaction of **1** (1.0 equiv.) with **2** (2.0 equiv.) was carried out. [b] Isolated yield. [c] Determined by GC-MS. [d] No reaction. [e] Aryl bromide was used.

The author briefly attempted to modify the resulting product **3f** in order to illustrate the synthetic scope of this methodology (Scheme 2). The author selected the stereoselective synthesis of the corresponding cis-β-fluorostyrene **4f**. Because if this transformation proceeds with complete retention of the configuration of the double bond, an overall reaction should afford a new stereoselective synthesis of cis-β-fluorostyrene derivatives.[10] Fortunately, the fluoride ion-assisted desilylation-protonation cleanly proceeded giving the desired product **4f**; however, the author encountered that the purification of **4f** from the crude reaction mixture on silica gel column chromatography proved to be more difficult due to their very close R_f values between **4f** and impurities. After many attempts, the transformation was accomplished by treatment with potassium tert-butoxide (*t*BuOK) in DMSO. The sequential purification of **4f** on silica gel column chromatography was conducted to give the desired **4f** in 99 % yield (Scheme 2).



3f **4f** (99%)

Scheme 2. Transformation of **3f** to the corresponding cis-fluoroolefin **4f**

2.3. Conclusion

In summary, the author has firstly developed the Mizoroki-Heck reaction of silylated fluoroolefin **1** with a wide range of aryl iodides in good to high yields. The desilylation-protonation reaction of the product cleanly proceeded affording the desired β-fluorostyrene derivative with very high stereoselectivity. This method should offer additional opportunities to be of help in fluoroorganic synthesis.

2.4. Experimental

2.4.1. General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^{1}H NMR and ^{13}C NMR spectra. On the other hand, chemical shifts were given by δ relative to that of $CFCl_3$ for ^{19}F NMR spectra using an internal $CF_3C_6H_5$ (benzotrifluoride) or C_6F_6. Infrared (IR) spectra are reported in cm^{-1}. Melting points are uncorrected.

2.4.2. Preparation of 3a

A 25 mL two-necked glass flask attached with a magnetic stir bar, a stopcock, and a three-way stopcock was successively charged with (1-fluorovinyl)methyldiphenylsilane **1** (47.5 mg, 0.196 mmol, 1.0 equiv.), 4'-iodoacetophenone **2a** (96.4 mg, 0.391 mmol, 2.0 equiv.), Ag_2CO_3 (162.1 mg, 0.606 mmol, 3.0 equiv.), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol,

10 mol %), and powdered MS4Å (ca. 160 mg) in 1,4-dioxane (1 mL). The whole resulting reaction mixture was generally heated at 90 ℃. When the reaction was completed for 4 h as monitored by GC-MS, the reaction mixture was cooled to room temperature. The cooled mixture was filtered off through celite pad with ether. After to the filtrate was added water, the organic layer was carefully separated. An additional extraction with hexane/EtOAc = 3/1 was repeated twice. The combined organic solution was dried over Na_2SO_4 and concentrated in vacuo. The resulting oily residue was first purified by column chromatography (silica gel, hexane/EtOAc = 10/1) to give the desired compound **3a** along with a small amount of impurities. The resulting oily residue was again purified by bulb-to-bulb distillation to give **3a** as a pale yellow solid (50.9 mg, 72 %).

2.4.3. Preparation of 4f

A 25 mL two-neck flask attached with a magnetic stir bar, a stopcock, and a three-way stopcock was successively charged with **3f** (72.9 mg, 0.209 mmol, 1.0 equiv.), *t*BuOK (34.7 mg, 0.309 mmol, 1.5 equiv.), and DMSO (1.0 mL) at room temperature. After the reaction was stirred for 1 h, the reaction mixture was quenched with water. After separation of the organic layer, additional extraction with hexane/EtOAc was repeated twice. The combined organic solution was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane/ether = 100/1) to give **4f** as a colorless oil (31.6 mg, 99 %)

2.4.4. Data of products (3a–3n, 4f)

(E)-[1-Fluoro-2-(4'-acetylphenyl)vinyl]methyldiphenylsilane (3a)

Pale yellow solid; yield 72 %; mp: 92.1–93.5 ℃; IR (KBr) 3069, 1680, 1601, 1489, 1355, 1266, 1184, 1115, 1044, 796, 736, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (d, *J* = 8.4 Hz, 2H) 7.66–7.60 (m, 6H), 7.49–7.36 (m, 6H), 5.97 (d, *J* = 50.3 Hz, 1H), 2.59 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.5, 169.4 (d, *J* = 295.8 Hz), 137.8 (d, *J* = 2.5 Hz), 135.9 (d, *J* = 2.5 Hz), 135.0, 133.0 (d, *J* = 1.2Hz), 130.2, 129.3 (d, *J* = 8.1 Hz), 128.2, 128.5, 122.4 (d, *J* = 1.9 Hz), 26.6, –5.0 (d, *J* = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –108.6 (d, *J* = 50.3 Hz); GC-MS (EI, *m*/*z*, 70 eV) 360 (3, M^+), 344 (7), 281 (8), 266 (14), 201 (59), 181 (22), 139 (100), 105 (19), 91 (44); Anal. Calcd. for $C_{23}H_21FOSi$: C, 76.63; H, 5.87. Found: C, 76.64; H, 5.89.

(E)-[1-Fluoro-2-[4'-(ethoxycarbonyl)phenyl]vinyl]methyldiphenylsilane (3b)

White solid; yield 63 %; mp: 71.1–72.7 ℃; IR (KBr) 3066, 2974, 1708, 1606, 1427, 1286, 1180, 1109, 1051, 1017, 784, 734, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.68–7.57 (m, 6H), 7.51–7.37 (m, 6H), 5.97 (d, *J* = 50.7 Hz, 1H), 4.37 (q, *J* = 7.16 Hz, 2H), 1.39 (t, *J* = 7.16 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1 (d, *J* = 295.2 Hz), 166.3, 137.5 (d, *J* = 2.5 Hz), 135.0, 133.0, 130.2, 129.6, 129.3 (d, *J* = 2.5 Hz), 129.1 (d, *J* = 8.1 Hz), 122.5 (d, *J* = 1.8 Hz), 60.9, 14.3, –5.0; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –109.2 (d, *J* = 50.7 Hz); GC-MS (EI, *m*/*z*, 70 eV) 348 (21), 286 (5), 255 (26), 231 (60), 201 (89), 169 (25), 139 (100), 105 (30), 91 (81), 77 (17); Anal. Calcd. for $C_{24}H_{23}FO_2Si$: C, 73.81; H, 5.94. Found: C, 74.00; H, 6.02.

(E)-[1-Fluoro-2-[4'-(nitrophenyl)vinyl]methyldiphenylsilane (3c)

Pale yellow solid; yield 81 %; mp: 87.9–89.0 ℃; IR (KBr) 3068, 1633, 1597, 1521, 1428, 1342, 1116, 1108, 1058, 824, 795, 735, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

8.17 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.63 (dd, *J* = 7.7, 1.8 Hz, 4H), 7.53–7.37 (m, 6H), 5.99 (d, *J* = 49.4 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0 (d, *J* = 299.0 Hz), 146.6 (d, *J* = 3.1 Hz), 139.5 (d, *J* = 3.1 Hz), 135.0, 132.5 (d, *J* = 1.2 Hz), 130.3, 129.8 (d, *J* = 8.7 Hz), 128.2, 123.7, 121.3 (d, *J* = 1.9 Hz), –5.0; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –113.6 (d, *J* = 49.4 Hz); GC-MS (EI, *m*/*z*, 70 eV) 347 (5), 286 (4), 255 (23), 231 (55), 201 (81), 178 (21), 165 (25), 139 (100), 105 (32), 91 (95); Anal. Calcd. for $C_{21}H_{18}FNO_2Si$: C, 69.40; H, 4.99; N 3.85. Found: C, 69.33; H, 4.96; N, 3.83.

(E)-[1-Fluoro-2-(4'-cyanophenyl)vinyl]methyldiphenylsilane (3d)

Pale yellow solid; yield 63 %; mp: 109.0–110.9 ℃; IR (KBr) 2229, 1588, 1505, 1488, 1428, 1255, 1109, 1049, 835, 800, 783, 733, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66–7.55 (m, 7H), 7.51–7.36 (m, 7H), 5.93 (d, *J* = 49.6 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4 (d, *J* = 297.7 Hz), 137.6 (d, *J* = 3.1 Hz), 135.0, 132.6, 132.1, 130.3, 129.6 (d, *J* = 8.7 Hz), 128.2, 121.3 (d, *J* = 1.9 Hz), 118.8, 110.9 (d, *J* = 3.1 Hz), –5.1; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –107.0 (d, *J* = 49.6 Hz); GC-MS (EI, *m*/*z*, 70 eV) 343 (2, M^+), 280 (4), 265 (15), 250 (14), 227 (7), 201 (66), 179 (15), 139 (100), 105 (19), 91 (47); HRMS (FAB, *m*/*z*) Calcd. for $C_{22}H_{19}NFSi$: 344.1295; Found: 344.1271.

(E)-[1-Fluoro-2-[4'-(trifluoromethyl)phenyl]vinyl]methyldiphenylsilane (3e)

Colorless oil; yield 77 %; IR (NaCl) 3071, 1617, 1489, 1430, 1326, 1168, 1115, 1068, 829, 794, 728, 698, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68–7.52 (m, 7H), 7.47–7.36 (m, 7H), 5.96 (d, *J* = 50.1 Hz, 1H), 0.81 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (d, *J* = 294.6 Hz), 136.6 (dq, *J* = 3.1, 1.3 Hz), 135.0, 133.1 (d, *J* = 1.9 Hz),

130.0, 129.6 (d, *J* = 2.5 Hz), 129.4 (d, *J* = 8.1 Hz), 128.2, 124.1 (q, *J* = 277.2 Hz), 125.3 (q, *J* = 3.7 Hz), 122.0 (d, *J* = 1.3 Hz), –4.96; ^{19}F NMR($CDCl_3$, 283 MHz) δ –109.5 (d, *J* = 50.1 Hz), –64.0; GC-MS (EI, *m*/*z*, 70 eV) 386 (1, M^+), 308 (10), 293 (11), 246 (20), 227 (55), 201 (92), 151 (55), 139 (100), 105 (41), 91 (76); Anal. Calcd. for $C_{22}H_{18}F_4Si$: C, 68.37; H, 4.69. Found: C, 68.66; H, 4.74.

(E)-[1-Fluoro-2-(4'-methoxyphenyl)vinyl]methyldiphenylsilane (3f)

White solid; yield 61 %; mp: 47.1–49.0 ℃; IR (KBr) 3011, 1606, 1506, 1428, 1251, 1180, 1117, 1044, 874, 829, 739, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, *J* = 7.7, 1.5 Hz, 4H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.46–7.34 (m, 6H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.87 (d, *J* = 51.8 Hz, 1H), 3.80 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2 (d, *J* = 286.5 Hz), 159.1 (d, *J* = 3.1 Hz), 135.0, 133.7 (d, *J* = 1.2 Hz), 130.7 (d, *J* = 8.1 Hz), 129.9, 128.0, 126.3 (d, *J* = 2.5 Hz), 123.0 (d, *J* = 1.3 Hz), 113.9, 55.2, –4.81 (d, *J* = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –117.3 (d, *J* = 51.8 Hz); GC-MS (EI, *m*/*z*, 70 eV) 348 (19, M^+), 286 (5), 255 (26), 231 (57), 201 (83), 178 (20), 165 (25), 139 (100), 105 (29), 91 (79); Anal. Calcd. for $C_{22}H_{21}FOSi$: C, 75.82;H, 6.07. Found: C, 75.82; H, 6.08.

(E)-[1-Fluoro-2-[2'-(fluorophenyl)vinyl]methyldiphenylsilane (3g)

Colorless oil; yield 70 %; IR (NaCl) 3071, 1579, 1482, 1429, 1231, 1117, 1100, 1054, 793, 755, 727, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02–7.93 (m, 1H), 7.64 (dd, *J* = 7.5, 1.8 Hz, 4H), 7.78–7.47 (m, 6H), 7.25–7.17 (m, 1H), 7.15–7.06 (m, 1H) 7.04–6.98 (m, 1H), 6.31 (d, *J* = 51.1 Hz, 1H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5 (dd, *J* = 293.3, 2.5 Hz), 159.3 (dd, *J* = 249.8, 1.2 Hz), 135.0, 133.2, 131.1 (dd, *J* = 13.7,

2.5 Hz), 130.1, 129.3 (dd, *J* = 8.7, 1.9 Hz), 128.1, 124.2 (d, *J* = 19.9 Hz), 121.1 (dd, *J* = 11.9, 2.5 Hz), 115.1 (d, *J* = 21.1 Hz), 114.4 (dd, *J* = 6.8, 1.8 Hz), –4.9; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –111.3 (dd, *J* = 51.1, 6.1 Hz, 1F), –117.6 (dt, *J* = 9.3, 6.1 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 336 (0.5, M^+), 254 (49), 239 (28), 201 (86), 178 (59), 165 (28), 152 (24), 139 (100), 105 (30), 91 (76); Anal. Calcd. for $C_{21}H_{18}F_2Si$: C, 74.97; H, 5.39. Found: C, 75.13; H, 5.39.

(E)-[1-Fluoro-2-(2'-chlorophenyl)vinyl]methyldiphenylsilane (3h)

Colorless oil; yield 88 %; IR (NaCl) 3070, 1589, 1429, 1254, 1115, 1052, 794, 728, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (dd, *J* = 7.7, 1.3 Hz, 1H) 7.65 (dd, *J* = 7.3, 1.5 Hz, 4H), 7.48–7.32 (m, 7H), 7.27–7.13 (m, 2H), 6.41 (d, *J* = 50.5 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2 (d, *J* = 294.6 Hz), 135.0, 133.2 (d, *J* = 1.2 Hz), 132.7 (d, *J* = 1.2 Hz), 131.3 (d, *J* = 12.4Hz), 131.1 (d, *J* = 2.5Hz), 130.1, 129.4, 128.8 (d, *J* = 1.2 Hz), 128.1, 126.7, 119.1 (d, *J* = 2.5 Hz), –4.93 (d, *J* = 1.3 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –113.3 (d, *J* = 50.5 Hz); GC-MS (EI, *m*/*z*, 70 eV) 352 (0.1, M^+), 254 (21), 239 (5), 223 (5), 212 (10), 201 (53), 178 (32), 139 (100), 105 (19), 91 (50); Anal. Calcd. for $C_{21}H_{18}ClFSi$: C, 71.47; H, 5.14. Found: C, 71.56; H, 5.13.

(E)-[1-Fluoro-2-(2'-bromophenyl)vinyl]methyldiphenylsilane (3i)

Colorless oil; yield 85 %; IR (NaCl) 3070, 1589, 1461, 1429, 1254, 1115, 1057, 1045, 793, 728, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ, 7.93 (dd, *J* = 7.7, 1.7 Hz, 1H) 7.65 (dd, *J* = 7.7, 1.8 Hz, 4H), 7.55 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.48–7.36 (m, 6H), 7.32–7.23 (m, 1H), 7.14–7.04 (m, 1H), 6.37 (d, *J* = 50.1 Hz, 1H), 0.81 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9 (d, *J* = 294.6 Hz), 135.0, 133.1 (d, *J* = 1.2 Hz), 132.73 (d, *J* = 12.4 Hz),

132.67, 131.4 (d, J = 20.5 Hz), 130.1, 129.0 (d, J = 1.3 Hz), 128.1, 127.3, 123.4 (d, J = 1.2 Hz), 121.9 (d, J = 3.2 Hz), –4.98 (d, J = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –114.0 (d, J = 50.1 Hz); GC-MS (EI, *m*/*z*, 70 eV) 397 (0.8, M^+), 317 (7), 302 (10), 255 (28), 239 (44), 223 (9), 201 (98), 178 (71), 139 (100), 91 (68); Anal. Calcd. for $C_{21}H_{18}BrFSi$: C, 63.48; H, 4.57. Found: C, 63.71; H, 4.58.

(E)-[1-Fluoro-2-[2'-(methoxycarbonyl)phenyl]vinyl]methyldiphenylsilane (3j)

Colorless oil; yield 60 %; IR (NaCl) 1721, 1598, 1429, 1080, 794, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92–7.82 (m, 1H), 7.66 (dd, J = 1.8, 7.5 Hz, 4H), 7.51–7.35 (m, 8H), 7.35–7.25 (m, 1H), 6.77 (d, J = 50.3 Hz, 1H), 3.75 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 167.8, 166.6 (d, J = 292.1 Hz), 135.1, 133.4 (d, J = 1.3 Hz), 133.3 (d, J = 4.4 Hz), 131.7, 131.3 (d, J = 9.4 Hz), 130.0, 129.0 (d, J = 1.3 Hz), 128.1, 127.3, 123.4 (d, J = 1.2 Hz), 121.6 (d, J = 3.2 Hz), 51.9, –5.0 (d, J = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –116.4 (d, J = 50.3 Hz); GC-MS (EI, *m*/*z*, 70 eV) 376 (0.2, M^+), 360 (4), 299 (37), 197 (64), 179 (100), 151 (37), 139 (34), 129 (41), 101 (25), 91 (42); Anal. Calcd. for $C_{23}H_{21}O_2FSi$: C, 73.37; H, 5.62. Found: C, 73.66; H, 5.76.

(E)-[1-Fluoro-2-(2'-ethylphenyl)vinyl]methyldiphenylsilane (3k)

Colorless solid; yield 65 %; mp: 46.0–48.0 ℃; IR (KBr) 3068, 2965, 1588, 1476, 1428, 1250, 1118, 1044, 757, 736, 700, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84–7.75 (m, 1H), 7.64 (dd, J = 7.7, 2.0 Hz, 4H), 7.47–7.36 (m, 7H), 7.22–7.11 (m, 2H), 6.12 (d, J = 50.6 Hz, 1H), 2.51 (q, J = 7.52 Hz, 2H), 1.08 (t, J = 7.52 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4 (d, J = 290.2 Hz), 141.8, 135.0, 133.6 (d, J = 1.9 Hz), 130.9 (d, J = 2.5 Hz), 130.2 (d, J = 10.0 Hz), 130.0, 128.6, 128.1, 128.0 (d, J = 1.2 Hz),

125.9, 121.0 (d, *J* = 1.3 Hz), 26.9, 15.0, –4.9; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –116.5 (d, *J* = 50.6 Hz); GC-MS (EI, *m*/*z*, 70 eV) 347 (11, M^+), 346 (35), 253 (6), 206 (23), 201 (61), 197 (48), 191 (12), 139 (100), 129 (26), 91 (22); Anal. Calcd. for $C_{23}H_{23}FSi$: C, 79.72; H, 6.69. Found: C, 79.71; H, 6.67.

(E)-[1-Fluoro-2-(3'-methoxyphenyl)vinyl]methyldiphenylsilane (3l)

Colorless oil; yield 78 %; IR (NaCl) 1599, 1428, 1256, 1115, 1050, 792, 670, 727, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, *J* = 1,8, 7.7 Hz, 4H), 7.47–7.35 (m, 6H), 7.27–7.07 (m, 3H), 6.98 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.91 (d, *J* = 51.0 Hz, 1H), 3.79 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1 (d, *J* = 291.4 Hz), 159.5, 135.0, 134.5 (d, *J* = 2.4 Hz), 133.4 (d, *J* = 1.3 Hz), 130.0, 129.3, 128.1, 123.3 (d, *J* = 1.9 Hz), 121.9 (d, *J* = 6.9 Hz), 114.3 (d, *J* = 8.1 Hz), 114.0 (d, *J* = 1.9 Hz), 55.2, –4.9 (d, *J* = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –112.6 (d, *J* = 51.0 Hz); GC-MS (EI, *m*/*z*, 70 eV) 348 (8, M^+), 332 (4), 269 (9), 254 (41), 201 (73), 178 (37), 165 (18), 139 (100), 105 (26), 91 (70); Anal. Calcd. for $C_{22}H_{21}FOSi$: C, 75.82; H, 6.07. Found: C, 75.78; H, 6.08.

(E)-[1-Fluoro-2-(2',4'-dimethylphenyl)vinyl]methyldiphenylsilane (3m)

Colorless oil; yield 67 %; IR (NaCl) 3070, 1613, 1589, 1429, 1253, 1116, 1053, 793, 728, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 7.5, 1.7 Hz, 4H), 7.45–7.34 (m, 6H), 7.01–6.94 (m, 2H), 6.07 (d, *J* = 49.2 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8 (d, *J* = 289.0 Hz), 137.5 (d, *J* = 1.2 Hz), 135.5, 135.0, 133.7, 130.8, 130.0, 129.8, 128,4 (d, *J* = 1.8 Hz), 128.0, 126.6, 121.0, 21.1, 19.9, –4.9 (d, *J* = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –116.4 (d, *J* = 49.2 Hz); GC-MS (EI, *m*/*z*, 70 eV) 347 (3, M^+), 253 (14), 229 (7), 201

(91), 181 (16), 165 (11), 152 (7), 139 (100), 105 (38), 91 (68); Anal. Calcd. for $C_{23}H_{23}FSi$: C, 79.72; H, 6.69. Found: C, 79.74; H, 6.71.

(E)-(1-Fluoro-2-phenylvinyl)methyldiphenylsilane (3n)

Colorless oil; yield 72 %; IR (NaCl) 3070, 3051, 3025, 1589, 1447, 1115, 1049, 793, 727, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67–7.59 (m, 7H), 7.58–7.51 (m, 2H), 7.47–7.35 (m, 7H), 5.96 (d, *J* = 50.1 Hz, 1H), 0.80 (s 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9 (d, *J* = 290.2 Hz), 135.0, 133.4 (d, *J* = 1.3 Hz), 133.3 (d, *J* = 2.5 Hz), 130.0, 129.3 (d, *J* = 7.4 Hz), 128.4, 128.1, 127.8 (d, *J* = 2.5 Hz), 123.4 (d, *J* = 1.9 Hz), –4.9 (d, *J* = 1.3 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ –106.1 (d, *J* = 50.1 Hz); GC-MS (EI, *m*/*z*, 70 eV) 318 (2, M^+), 302 (5), 255 (11), 239 (31), 225 (39), 201 (97), 178 (84), 139 (100), 105 (30), 91 (56); HRMS (FAB, *m*/*z*) Calcd. for $C_{21}H_{19}FSi$: 318.1240; Found: 318.1209.

(Z)-1-Fluoro-2-(4'-methoxyphenyl)ethene (4f)[10a]

Colorless oil; yield 99 %; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.59 (dd, *J* = 82.9, 5.3 Hz, 1H), 5.54 (dd, *J* = 35.1, 5.3 Hz, 1H), 3.81 (s, 3H).

2.5. References

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Chapter three

Synthesis of 2-Aryl-3-fluoro-5-silylthiophenes via Cascade Reactive Sequence

3.1. Introduction

Organofluorine chemistry has recently made great progress in medicinal and agricultural fields. On the other hand, heteroaromatic chemistry has a long unique history in the similar fields. The thiophene nucleus was representative for a component of several classes of bioactive natural compounds and functional materials.[1] Therefore, a easy synthesis for fluorinated thiophenes still remains a challenging task. By literature survey, there are only a few procedures for the preparation of fluorinated thiophenes despite the fact that fluoro substituents are powerful modifiers of chemical and biological properties of organic molecules as reported in many pharmaceuticals and agrochemicals.[2] There are a lot of methods for the synthesis of fluorinated thiophenes based on an application of the substitution reactions of fluorine on the thiophene ring.[3] In contrast to these traditional methods, few are alternative synthetic strategy for the regioselective synthesis of fluorinated thiophenes via cyclization process. To the best of my knowledge, only three groups have reported this methodology for the synthesis of substituted fluorothiophenes.[4] Our group has been interested in the building block strategy for introduction of fluorine(s) into organic molecules.[5] To expand the synthetic possibility of 2-bromo-3,3,3-trifluoropropene **1** as a starting material, the

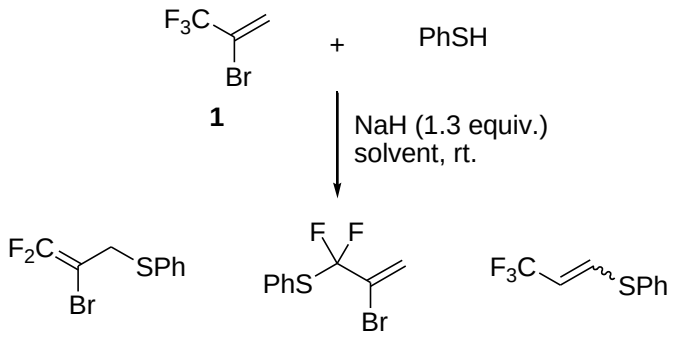
author focused on its S_N2'-type reaction. The author found that the similar S_N2'-type reactions have already been reported by several groups in the literature.[6] Among them, there was only one example of using 2-bromo-3,3,3-trifluoropropene.[7] The author describes here the first efficient S_N2'-type reactions of **1** with various thiolates, giving highly selective 2-bromo-3,3-difluoroallyl sulfides **2**. In addition, the author explained the step-wise synthesis of 2-aryl-3-fluoro-5-silylthiophenes **10** in high yield in the latter part.

3.2. Results and discussion

The author initially investigated a S_N2'-type reaction of **1** and thiophenol under various reaction conditions (Table 1). According to the previous reported procedure, when the reaction of **1** (3.0 equiv.) and thiophenol (1.0 equiv.) was carried out in THF in the presence of NaH (1.3 equiv.), the desired S_N2'-type product **2a** was obtained along with an unexpected structural isomer **3a**, with a ratio of **2a**/**3a** = 80/20 in 57 % combined yield. Unfortunately, the author figured out that this mixture was unable to be separated into its components. The author determined the structures of **2a** and **3a** on the basis of their ^{1}H and ^{19}F NMR. The author considered that the product **3a** was probably formed via an excessive S_N2'-type reaction of **2a** with thiophenoxide. With this consideration in mind, the author continued to determine the optimal reaction conditions. As a result, when this reaction was performed in 1,4-dioxane for 6 h, the selectivity was improved to afford the products with a ratio of **2a**/**3a** = 93/7 in 73 % combined yield. Increasing or decreasing the amount of **1** influenced the product

selectivity to some extent. The author observed that lowering the amount of **1** to 1.0 equivalents resulted in the slightly lower selectivity, whereas increasing that of **1** to 5.0 equivalents resulted in the slightly higher selectivity. Interestingly, other tested solvents retarded the formation of the desired product **2a**.

Table 1. Reaction of **1** and thiophenol under various conditions



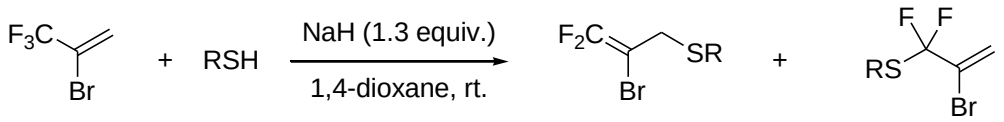
entry	**1** (equiv.)	solvent	time (min)	Yield[b] (%)	**2a**/**3a**/**4a**[c]
1	3.0	THF	60	57	80/20/0
2	3.0	1.4-dioxane	360	73	93/7/0
3	1.0	1.4-dioxane	360	66	87/13/0
4	5.0	1.4-dioxane	360	69	96/4/0
5	3.0	DMF	10	trace[d]	-
6	3.0	DMSO	10	trace[d]	-
7	3.0	CH_3CN	10	trace[d]	-
8	3.0	Et_2O	240	NR[e]	-
9	3.0	toluene	240	NR[e]	-
10[f]	1.2	EtOH	480	94	0/0/100

[a] The reaction of **1** with PhSH (1.0 equiv) was carried out. [b] Isolated combined yield. [c] The ratio was determined by ^{19}F NMR spectroscopy. [d] Major products were **4a**. [e] No reaction. [f] KOH was used instead of NaH. See ref 5.

As the author determined the optimized reaction conditions, the substrate scope was next examined using 3.0 equivalents of **1** and various thiols in the presence of NaH (1.3 equiv.) at room temperature. Table 2 shows that the reaction smoothly proceeded with

a variety of substrates, affording the corresponding S_N2'-type product **2b**–**2l** in good to high yields with high to excellent selectivity. The author addressed that the alkylthiols gave the corresponding S_N2'-type products exclusively, in sharp contrast to arylthiols. From these findings, the author proposed that one factor for the occurrence of excessive S_N2'-type reaction of **2** might be associated with the p*K*a value of thiols.

Table 2. Substrate scope of S_N2'-type reaction of **1**[a]



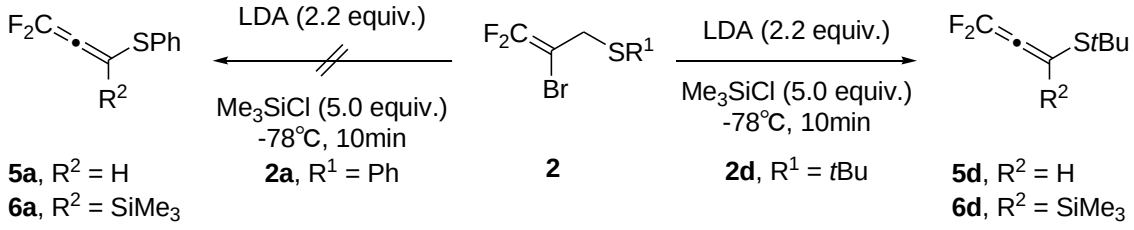
1 **2b**-**2l** **3b**-**3l**

entry	R	time (h)	**2**	yield[b] (%)	**2**/**3**[c]
1	2,4-MeC_6H_3	6	**2b**	84	94/6
2	*n*$C_{12}H_{25}$	6	**2c**	82	>99/1
3	*t*Bu	3	**2d**	75	99/1
4	Ph_3C	3	**2e**	86	99/1
5	$PhCH_2CH_2$	18	**2f**	82	99/1
6	$PhCH_2$	3	**2g**	88	99/1
7	4-Me-$C_6H_4CH_2$	7	**2h**	78	>99/1
8	4-Cl-$C_6H_4CH_2$	7	**2i**	73	99/1
9	4-MeO-$C_6H_4CH_2$	7	**2j**	75	>99/1
10	2-Cl-$C_6H_4CH_2$	4	**2k**	79	99/1
11	2,4,6-Me-$C_6H_2CH_2$	6	**2l**	77	>99/1

[a] The reaction of **1** (3.0 equiv.) with RSH (1.0 equiv.) was carried out. [b] Isolated yield. [c] The ratio was determined by ^{19}F NMR spectroscopy.

The author then examined synthetic applications of the obtained products **2**. Although *gem*-difluoroallenes have greatly attracted attention due to their potential as difluorinated synthons, there is few the related study on the convenient synthesis of functionalized *gem*-difluoroallenes.[8] Therefore, the author set out the examination of the synthesis of *gem*-difluoroallenyl sulfide from 2-bromo-3,3-difluoroallyl sulfide via a proper elimination reaction. The author conducted the preliminary experiment with a slight excess amount of LDA (1.2 equiv.) in THF at –78 °C. Unfortunately, the reaction resulted in the decomposition of **2a** along with recovery of the unreacted starting material **2a**. There was no desired *gem*-difluoroallenyl sulfide **5a** in the reaction mixture. Then, the author employed **2d** instead of **2a** in the similar reaction conditions, which also led to a similar result. Careful observation in these reactions made the author be aware of the incomplete consumption of **2a** in spite of the excessive use of LDA. This finding encouraged me to speculate that prior to full deprotonation of **2a** by LDA, the produced product **5a** might undergo next deprotonation process to generate the corresponding allenyl anion which may easily decompose. To confirm this working hypothesis, the author performed the reaction of **2a** with LDA (2.2 equiv.) in the presence of an excess amount of Me_3SiCl (5.0 equiv.) in order to trap the generated allenyl anion. The author found that the expecting reaction turned out to be complicated and the resulting mixture gave a lot of peaks by GC-MS analysis. The author observed that the reaction of **2d** instead of **2a** gave the *gem*-difluorosilylallenyl sulfide **6d** in the reaction mixture by GC-MS. The main GC-MS peak appeared at *m/z* = 179 (M^+–*t*Bu) [MW = 236 ($C_{10}H_{18}F_2SSi$)], which would probably correspond to the structure of **6d**. In order to get more information the author quenched the reaction and extracted the organic compounds. The residual oil was purified by distillation to give

6d along with a small amount of inevitable contaminants. The structure of **6d** was supported by ^{19}F and ^{13}C NMR spectra. Both typical terminal fluorine signals appeared at –103.5 ppm (s). The central *sp*-carbon was appeared at 165.3 ppm (t, J = 35.1 Hz) and two sp^2-carbons at two ends of allenyl moiety appeared at 156.4 ppm (t, J = 259.3 Hz) and 134.4 ppm (t, J = 7.0 Hz) (Scheme 1). Although the author purified the product using silica gel column chromatography, the process resulted in the decomposition of **6d** as observed by multiple peaks in GC-MS analysis.



5a, R^2 = H
6a, R^2 = $SiMe_3$

2a, R^1 = Ph

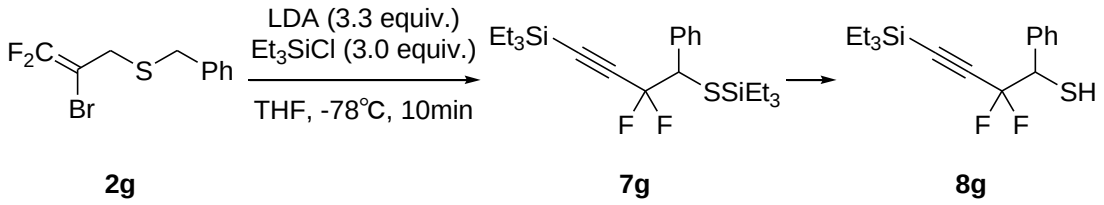
2

2d, R^1 = *t*Bu

5d, R^2 = H
6d, R^2 = $SiMe_3$

Scheme 1. Reaction of **2a** and **2d** with LDA in the presence of Me_3SiCl

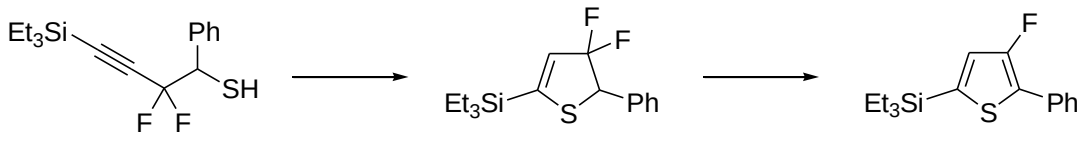
Interestingly, when the author conducted the reaction of **2g** with LDA (2.2 equiv.) in the presence of Et_3SiCl (2.0 equiv.) in THF at –78 °C for 10 min, only one new peak in GC-MS analysis at m/z = 397 (M^+–Et) [MW = 426 ($C_{22}H_{36}F_2SSi_2$)] was observed. The later check of the reaction mixture would suggest the structure of **7g** together with the unreacted **2g** (ca. 40 %). No complete consumption of the remaining **2g** occurred while stirring at room temperature for prolonged reaction time. In order to complete consumption of **2g** the author performed a similar reaction with excess LDA (3.3 equiv.) in the presence of excess Et_3SiCl (3.0 equiv.). The reaction smoothly proceeded to provide the unexpected *gem*-difluorohomoproparygyl thiol **8g** in 82 % yield as a desilylated product of **7g** after silica gel column purification (Scheme 2).



2g **7g** **8g**

Scheme 2. Synthesis of *gem*-difluorohomopropargyl thiol **8g**

The structure of **8g** was determined by ^{1}H, ^{13}C and ^{19}F NMR spectra and FT-IR. The methine proton signal of **8g** was observed at 4.4 ppm (ddd, J = 12.3, 8.2, 6.4 Hz). Two sp-carbon signals appeared at 94.4 ppm (t, J = 4.7 Hz) and 96.1 (t, J = 39.0 Hz). Two signals of the geminal fluorines were observed at –85.0 ppm (dd, J = 267.0, 8.2 Hz) and –88.0 ppm (dd, J = 267.0, 12.2 Hz). The characteristic peak at 2186 cm^{-1} in the FT-IR spectrum was assigned to CC triple bond stretching vibrations. Unfortunately, the author noticed that this g*em*-difluorohomoproparygyl thiol **8g** gradually turned yellow at room temperature after solvent removal, giving many peaks by GC-MS because of its unstable nature. However, the author noticed that the promising transformation occurred from **8g** to the novel fluorinated thiophene **10ga** via the corresponding 3,3-difluorodehydrothiophene **9g** (Scheme 3).[9]



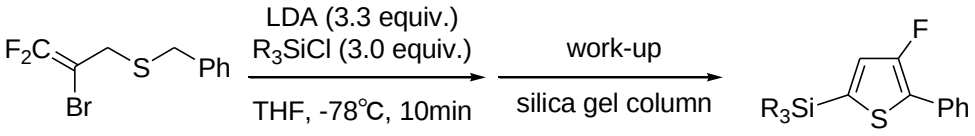
8g **9g** **10ga**

Scheme 3. Synthesis of 2-phenyl-3-fluoro-5-triethylsilylthiophene **10ga**

On the basis of these findings, the author started to examine the overall transformation

reaction from **2g** to **10ga**. Table 3 shows the selected reaction conditions of this one-pot synthesis of 3-fluorothiophene derivative **10g**.

Table 3. Screening of one-pot reaction conditions of **2g**[a]



2g **10g**

entry	R_3SiCl	work-up	additive	**10g**	Yield[b] (%)
1	Et_3SiCl	sat. $NaHCO_3$	Et_3N	**10ga**	82
2	Et_3SiCl	sat. NaCl	none	**10ga**	79
3	Et_3SiCl	sat. NaCl	Et_3N	**10ga**	83
4	Me_3SiCl	sat. NaCl	Et_3N	**10gb**	79
5	$PhMe_2SiCl$	sat. NaCl	Et_3N	**10gc**	70[c]
6	$Ph_2MeSiCl$	sat. NaCl	Et_3N	**10gd**	45[d]

[a] **2g** (1.0 equiv.) and additive (1.0 equiv.) were used. [b] Isolated yield. [c] 93 % Purity. [d] The corresponding desilylated 3-fluorothiphene derivatives **10ge** was isolated in 29 %.

After much screening of reaction parameters (including chlorosilane, work-up, and the additive), the author focused on the following three factors for generating 2-phenyl-3-fluoro-5-triethylsilylthiophene **10ga** in 83 % chemical yield (entry 3): (1) Chlorotriethylsilane (Et_3SiCl) as an electrophile was the best. (2) It is necessary that the direct addition of aqueous sodium chloride solution to the reaction mixture at –78 °C was suitable for quenching the reaction. (3) The presence of triethylamine plays an important role for successive cyclization reaction. It is beneficial that this one-pot

protocol requires only one time silica gel chromatographic purification.

With the optimized reaction conditions in hand, the author examined the scope of this one-pot 3-fluorothiophene in order to synthesis of a series of 2-bromo-3,3-difluoroallyl sulfides **2f**–**2l**. Regardless of the sulfides **2h**–**2k**, the reaction similarly proceeded to give the corresponding 3-fluorothiophene derivative **10ha**–**10ka** in high yields, respectively (Figure 1). On the contrary, when the author conducted the reaction of **2f** and **2l** under the identical conditions no desired 3-fluorothiophene derivatives obtained but the corresponding *gem*-difluoroallene derivatives **5f** and **5l** did.

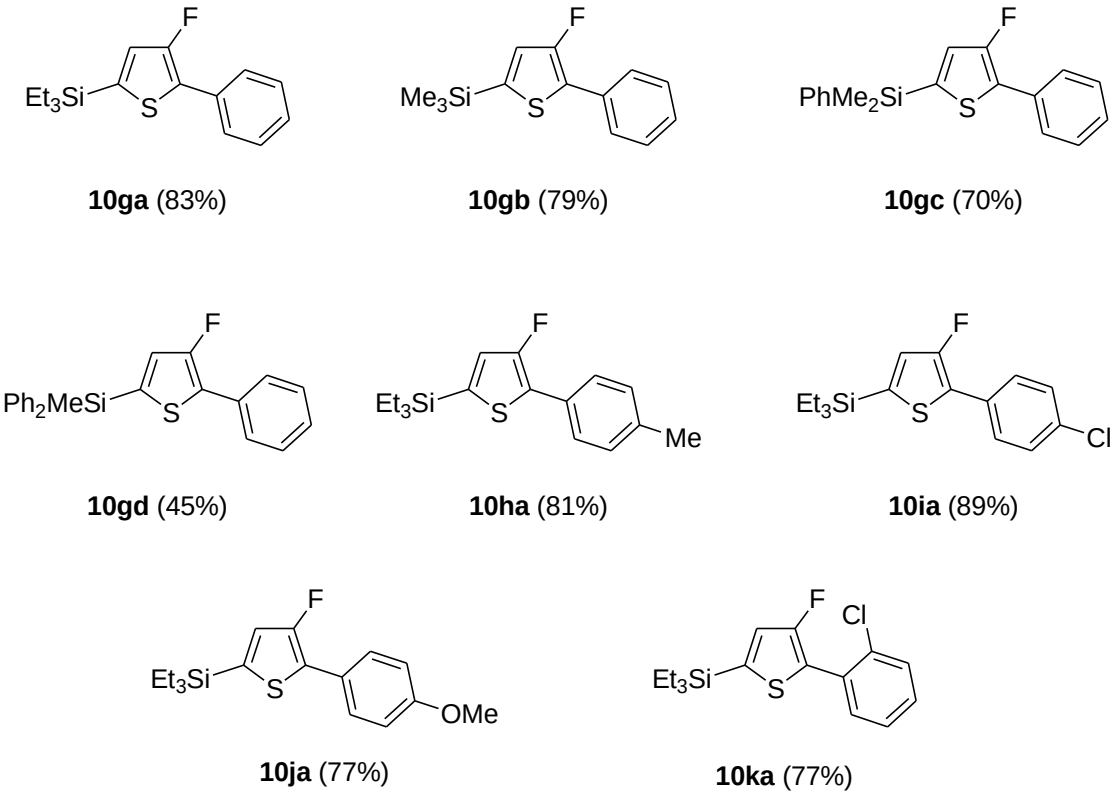
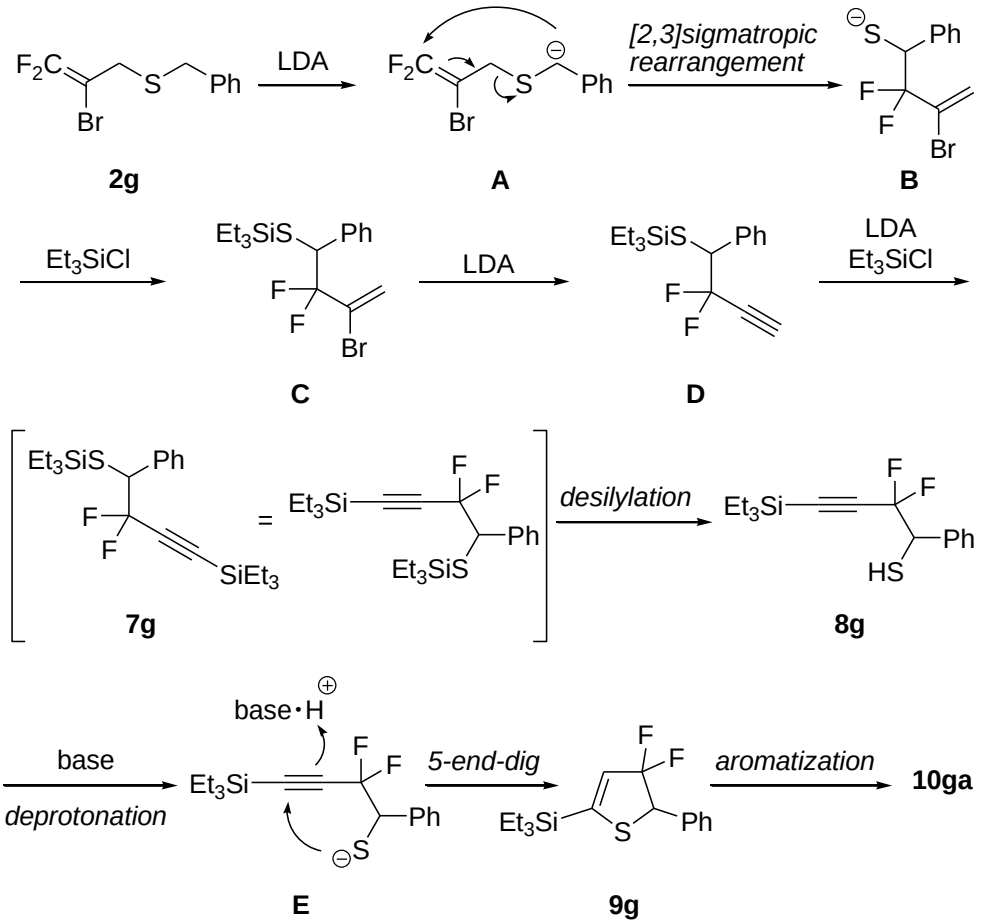


Figure 1. 2-Aryl-3-fluoro-5-silylthiophenes **10**

On the basis of these experimental results, the author proposed the plausible reaction mechanism postulated in Scheme 4. Initially, 2-bromo-3,3-difluoroallyl benzyl sulfide

2g undergoes deprotonation at the benzylic position instead of the allylic position, followed by [2,3]sigmatropic rearrangement to produce the corresponding *gem*-difluorohomopropargyl thiolate **B**.[10] At this point, the silylated product **C** as possible intermediates have not been observed. The bromoethylene moiety of the silylated product **C** was then transformed into the terminal acetylene by LDA followed by silylation at the terminal carbon to yield the product **7g**. Successive desilylation of **7g** under aqueous basic conditions proceeds to give the free *gem*-difluorohomopropargyl thiol **8g**. The resulting thiol **8g** undergoes similar intramolecular cyclization in a *5-endodig* fashion, as reported by Hammond.[11] Finally, the resulting 4,4-difluoro-3,4-dihydrothiophene **9g** easily undergoes aromatization on the silica gel column chromatography yielding the 3-fluorothiophene **10ga**.



Scheme 4. Plausible reaction mechanism for 3-fluorothiophene formation

3.3. Conclusion

In summary, the author has developed the first successful S_N2'-type reaction of 2-bromo-3,3,3-trifluoropropene **1** and a wide range of thiols. The reaction opens the new route to provide the corresponding 2-bromo-3,3-difluoroallyl sulfides **2** in good to high yields with high to excellent selectivity. In addition, the resulting 2-bromo-3,3-difluoroallyl benzyl sulfides are efficiently transformed into the novel 2-aryl-3-fluoro-5-triethylsilylthiophenes **10** in high yields.

3.4. Experimental

3.4.1. General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^{1}H NMR and ^{13}C NMR spectra. On the other hand, chemical shifts were given by δ relative to that of $CFCl_3$ for ^{19}F NMR spectra using an internal $CF_3C_6H_5$ (benzotrifluoride) or C_6F_6. Infrared (IR) spectra are reported in cm^{-1}. Melting points are uncorrected.

3.4.2. Preparation of 2g

A 25 mL two-neck flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with 1 mL of hexane under argon. To this solution was added NaH (63 % dispersion in mineral oil, 21.3 mg, 0.559 mmol, 1.3 equiv.). After stirring for several minutes, the solvent was removed by syringe. To this flask was added 1 mL of 1,4-dioxane and benzylthiol (50.0 μL, 0.433 mmol, 1.0 equiv.). After the mixture was stirred for 10 min at room temperature, the flask was immersed in an ultrasonic wave for 30 min and a cloudy white solution formed. To this mixture was added 2-bromo-3,3,3-trifluoropropene (133 μL, 1.28 mmol, 3.0 equiv.) and stirred at room temperature until the complete consumption of benzylthiol (checked by GC-MS). To the mixture was added water (3 mL) and the resulting mixture was extracted with hexane (2 mL) three times. The combined solution was dried over sodium sulphate, concentrated in vacuo then the residual oil was purified by chromatography on silica gel column (hexane as an eluent) to give **2g** (105.6 mg, 88 %) as colorless oil.

3.4.3. Preparation of 10ga

A solution of *N*,*N*-diisopropylamine (357 μL, 2.55 mmol, 3.3 equiv.) in THF (3 mL) was cooled to 0 °C and treated with *n*BuLi (1.57 mL of 1.62 M solution in hexane, 2.55 mmol, 3.3 equiv.). The resulting solution was cooled to –78 °C and to this solution was added Et_3SiCl (389 μL, 2.32 mmol, 3.0 equiv.). After 10 min, the solution was treated drop-wise with **2g** (215.7 mg, 0.773 mmol, 1.0 equiv.) in THF solution. The reaction mixture was stirred for 10 min, and then quenched with saturated aqueous solution of NaCl (3 mL) at –78 °C. To the resulting solution was added triethylamine (108 μL, 0.773 mmol, 1.0 equiv.) at this temperature and the mixture was gradually warmed to room temperature. After stirring for 1 day, the mixture was extracted with hexane/ether = 3/1 (2 mL) three times. The combined solution was dried over sodium sulphate, concentrated in vacuo then the residual oil was purified by chromatography on silica gel column (hexane as an eluent) to give **10ga** (187.8 mg, 83 %) as colorless oil.

3.4.4. Data of products (2a–2l, 10ga-10ge, 10ha-10ka)

(2-bromo-3,3-difluoroallyl)(phenyl)sulfane (2a)

Colorless oil; yield 73 %; IR (NaCl) 3060, 1734, 1480, 1439, 1281, 1195, 1139, 979, 744, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.44 (m, 2H), 7.34–7.29 (m, 3H), 3.77–3.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.1 (dd, *J* = 291.1, 287.2 Hz), 136.6, 132.7, 129.0, 128.0, 78.3 (dd, *J* = 36.6, 21.8 Hz), 37.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –83.0 (d, *J* = 34.5 Hz, 1F) –88.7 (d, *J* = 34.5 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 266 (32, $M^+[^{81}Br]$), 264 (31, $M^+[^{79}Br]$), 185 (93), 165 (100), 157 (72), 155 (73), 131 (15), 129 (15), 109 (95), 65 (33).

(2-bromo-3,3-difluoroallyl)(2,4-dimethylphenyl)sulfane (2b)

Colorless oil; yield 84 %; IR (NaCl) 2923, 1734, 1603, 1479, 1280, 1195, 1139, 979, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 0.6 Hz, 1H), 6.98–6.94 (m, 1H), 3.67–3.65 (m, 2H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.0 (dd, *J* = 291.1, 287.2 Hz), 140.8, 138.4, 134.1, 131.2, 128.6, 127.2, 78.2 (dd, *J* = 36.6, 21.8 Hz), 36.7, 21.0, 20.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –83.2 (d, *J* = 34.1 Hz), –89.1 (d, *J* = 34.1 Hz); GC-MS (EI, *m*/*z*, 70 eV) 294 (45, $M^+[^{81}Br]$), 292 (44, $M^+[^{79}Br]$), 213 (49), 193 (51), 157 (11), 155 (13), 137 (100), 93 (17), 91 (34), 77 (20).

(2-bromo-3,3-difluoroallyl)(dodecyl)sulfane (2c)

Colorless oil; yield 82 %; IR (NaCl) 2976, 2854, 1733, 1466, 1277, 1135, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.46 (dd, *J* = 2.8, 2.0 Hz, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.64–1.55 (m, 2H), 1.56–1.19 (m, 18H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8 (dd, *J* = 290.3, 287.2 Hz), 79.1 (dd, *J* = 37.3, 21.1 Hz), 33.0, 31.9, 31.4, 29.61, 29.60, 29.50, 29.3, 29.15, 29.12, 28.8, 22.7, 14.1; ^{19}F NMR ($CDCl_3$, 283 MHz) δ –83.4 (dt, *J* = 38.3, 2.0 Hz, 1F), –89.3 (dt, *J* = 38.3, 2.8 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 358 (1, $M^+[^{81}Br]$), 356 (1, $M^+[^{79}Br]$), 201 (100), 157 (15), 155 (15), 111 (4), 97 (9), 83 (11), 69 (16), 55 (15); Anal. Calcd. for $C_{15}H_{27}BrF_2S$: C, 50.42; H, 7.62. Found: C, 50.68; H, 7.64.

tert-butyl(2-bromo-3,3-difluoroallyl)sulfane (2d)

Colorless oil; yield 75 %; IR (NaCl) 2964, 1737, 1459, 1365, 1277, 1184, 1137, 975cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.53–3.49 (m, 2H), 1.36 (s, 9H); ^{13}C NMR

($CDCl_3$, 101 MHz) δ 153.0 (dd, *J* = 290.3, 286.5 Hz), 79.6 (dd, *J* = 37.4, 21.8 Hz), 43.0, 30.8, 30.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –83.5 (d, *J* = 38.1 Hz, 1F), –88.3–(–88.5) (m, 1F); GC-MS (EI, *m*/*z*, 70 eV) 246 (29, $M^+[^{81}Br]$), 244 (29, $M^+[^{79}Br]$), 157 (21), 155 (22), 139 (3), 137 (3), 131 (7), 129 (7), 75 (8), 57 (100); Anal. Calcd. for $C_7H_{11}BrF_2S$: C, 34.30; H, 4.52. Found: C, 34.49; H, 4.60.

(2-bromo-3,3-difluoroallyl)(trityl)sulfane (2e)

White solid; yield 86 %; mp: 92.0–93.3 ℃; IR (KBr) 3028, 1745, 1593, 1487, 1444, 1278, 1185, 1139, 980, 744, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.40 (m, 6H), 7.33–7.20 (m, 9H), 3.11–3.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.3 (dd, *J* = 291.9, 286.5 Hz), 144.1, 129.5, 128.0, 76.8 (dd, *J* = 38.1, 23.1 Hz), 67.2, 33.3, 128; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.6 (d, *J* = 34.1 Hz, 1F), –86.9–(–87.2) (m, 1F); Anal. Calcd. for $C_{22}H_{17}BrF_2S$: C, 61.26; H, 3.97. Found: C, 61.27; H, 3.97.

(2-bromo-3,3-difluoroallyl)(phenethyl)sulfane (2f)

Colorless oil; yield 82 %; IR (NaCl) 3004, 2921, 1733, 1497, 1454, 1278, 1134, 979, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.28 (m, 2H), 7.26–7.18 (m, 3H), 3.48–3.45 (m, 2H), 2.92–2.86 (m, 2H), 2.79–2.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.9 (dd, *J* = 290.4, 288.1 Hz), 140.0, 128.5, 128.4, 126.5, 78.9 (dd, *J* = 36.6, 21.0 Hz), 35.9, 33.1, 32.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –83.0 (d, *J* = 35.4 Hz, 1F), –88.8 (d, *J* = 35.4 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 294 (25, $M^+[^{81}Br]$), 292 (25, $M^+[^{79}Br]$), 203 (25), 201 (15), 157 (34), 155 (35), 137 (33), 104 (41), 91 (100), 77 (16); Anal. Calcd. for $C_{11}H_{11}BrF_2S$: C, 45.07; H, 3.78. Found: C, 45.19; H, 3.72.

benzyl(2-bromo-3,3-difluoroallyl)sulfane (2g)

Colorless oil; yield 88 %; IR (NaCl) 2922, 1733, 1494, 1453, 1408, 1278, 1196, 1134, 980, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.25 (m, 5H), 3.73 (s, 2H), 3.39–3.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6 (dd, *J* = 290.9, 287.8 Hz), 137.3, 128.8, 128.5, 127.2, 79.0 (dd, *J* = 36.7, 21.2 Hz), 35.9, 32.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.8 (d, *J* = 36.7 Hz, 1F), –88.1 (d, *J* = 36.7 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 280 (8, $M^+[^{81}Br]$), 278 (8, $M^+[^{79}Br]$), 179 (2), 157 (2), 155 (2), 131 (2), 129 (2), 122 (5), 91 (100), 77(5); HRMS (FAB, *m*/*z*) Calcd. for $C_{10}H_9BrF_2S$: 277.9576; Found: 277.9565.

(4-methylbenzyl)(2-bromo-3,3-difluoroallyl)sulfane (2h)

Colorless oil; yield 78 %; IR (NaCl) 2921, 1733, 1514, 1277, 1196, 1134, 980, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 3.69 (s, 2H), 3.37–3.34 (m, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.6 (dd, *J* = 290.4, 287.2 Hz), 136.9, 134.1, 129.2, 128.8, 79.1 (dd, *J* = 37.4, 21.8 Hz), 35.5, 32.3, 21.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.9 (d, *J* = 35.7 Hz, 1F), –88.1 (d, *J* = 35.7 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 294 (14, $M^+[^{81}Br]$), 292 (13, $M^+[^{79}Br]$), 157 (2), 155 (2), 137 (3), 135 (3), 105 (100), 103 (7), 91 (6), 77 (9); Anal. Calcd. for $C_{11}H_{11}BrF_2S$: C, 45.07; H, 3.78. Found: C, 45.02; H, 3.76.

(4-chlorobenzyl)(2-bromo-3,3-difluoroallyl)sulfane (2i)

Colorless oil; yield 73 %; IR (NaCl) 2836, 1733, 1611, 1512, 1277, 1249, 1176, 1035, 980, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.25 (m, 4H), 3.69 (s, 2H), 3.37–3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.6 (dd, *J* = 291.2, 288.0 Hz),

135.8, 133.0, 130.2, 128.7, 78.8 (dd, *J* = 36.6, 21.0 Hz), 35.0, 32.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.6 (d, *J* = 35.4 Hz, 1F), –88.0 (d, *J* = 35.4 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 316 (5, $M^+[^{81}Br]$), 314 (17, $M^+[^{79}Br]$), 312 (13), 157 (6), 155 (6), 127 (34), 125 (100), 99 (4), 89 (12), 75 (5); Anal. Calcd. for $C_{10}H_8BrClF_2S$: C, 38.30; H, 2.57. Found: C, 38.46; H, 2.47.

(4-methoxybenzyl)(2-bromo-3,3-difluoroallyl)sulfane (2j)

Colorless oil; yield 75 %; IR (NaCl) 2920, 1732, 1592, 1490, 1442, 1407, 1278, 1197, 1135, 1093, 1015, 981, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 2H), 3.37–3.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.7, 153.6 (dd, *J* = 290.4, 287.2 Hz), 129.9, 129.1, 113.9, 79.1 (dd, *J* = 36.6, 21.0 Hz), 55.2, 35.1, 32.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.9 (d, *J* = 35.4 Hz, 1F), –88.2 (d, *J* = 35.4 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 310 (8, $M^+[^{81}Br]$), 308 (8, $M^+[^{79}Br]$), 155 (2), 153 (2), 138 (2), 121 (100), 109 (4), 107 (2), 91 (4), 77 (7); Anal. Calcd. for $C_{11}H_{11}BrF_2OS$: C, 42.73; H, 3.59. Found: C, 42.84; H, 3.52.

(2-chlorobenzyl)(2-bromo-3,3-difluoroallyl)sulfane (2k)

Colorless oil; yield 79 %; IR (NaCl) 3020, 2926, 1733, 1472, 1444, 1279, 1196, 1135, 981, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.30 (m, 2H), 7.28–7.19 (m, 2H), 3.85 (s, 2H), 3.46–3.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.7 (dd, *J* = 290.4, 287.2 Hz), 135.0, 134.2, 130.5, 129.9, 128.7, 126.8, 78.9 (dd, *J* = 36.6, 21.0 Hz), 33.4, 32.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –82.5 (d, *J* = 36.8 Hz, 1F), –88.1 (d, *J* = 36.8 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 316 (5, $M^+[^{81}Br]$), 314 (19, $M^+[^{79}Br]$), 312 (14), 157 (7), 156 (6), 155 (6), 127 (34), 125 (100), 89 (12), 75 (6); Anal. Calcd. for $C_{10}H_8BrClF_2S$: C,

38.30; H, 2.57. Found: C, 38.43; H, 2.58.

(2,4,6-trimethylbenzyl)(2-bromo-3,3-difluoroallyl)sulfane (2l)

White solid; yield 77 %; mp: 38.1–38.8 ℃; IR (KBr) 2920, 1733, 1613, 1278, 1193, 1134, 978, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.84 (s, 2H), 3.75 (s, 2H), 3.55–3.52 (m, 2H), 2.39 (s, 6H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.8 (dd, *J* = 290.3, 287.2 Hz), 137.1, 136.9, 129.6, 129.0, 79.0 (dd, *J* = 37.4, 21.0 Hz), 34.2, 30.8, 20.9, 19.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –83.3 (d, *J* = 36.7 Hz, 1F), –88.7 (d, *J* = 36.7 Hz, 1F); GC-MS (EI, *m*/*z*, 70 eV) 266 (32, $M^+[^{81}Br]$), 264 (31, $M^+[^{79}Br]$), 185 (93), 165 (100), 157 (72), 155 (73), 131 (15), 129 (15), 109 (95), 65 (33); Anal. Calcd. for $C_{13}H_{15}BrF_2S$: C, 48.61; H, 4.71. Found: C, 48.83; H, 4.65.

triethyl(4-fluoro-5-phenylthiophen-2-yl)silane (10ga)

Colorless oil; yield 82 %; IR (NaCl) 2956, 2876, 1602, 1555, 1495, 1360, 1237, 1016, 963, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66–7.60 (m, 2H), 7.41–7.30 (m, 2H), 7.23–7.20 (m, 1H), 6.97 (s, 1H), 1.02 (t, *J* = 7.8 Hz, 9H), 0.82 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.1 (d, *J* = 263.9 Hz), 133.7 (d, *J* = 4.7 Hz), 131.5 (d, *J* = 3.9 Hz), 128.7, 127.3, 126.6 (d, *J* = 5.4 Hz), 126.3 (d, *J* = 13.2 Hz), 125.4 (d, *J* = 24.9 Hz), 7.2, 4.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.9 (s); GC-MS (EI, *m*/*z*, 70 eV) 292 (64, M^+), 263 (79), 235 (66), 207 (100), 191 (3), 173 (3), 158 (4), 127 (6), 118 (6), 104 (11); Anal. Calcd. for $C_{16}H_{21}FSSi$: C, 65.70; H, 7.24;. Found: C, 65.78; H, 7.20.

(4-fluoro-5-phenylthiophen-2-yl)trimethylsilane (10gb)

Colorless oil; yield 79 %; IR (NaCl) 2957, 2896, 1602, 1573, 1557, 1494, 1362, 1251,

1035, 963, 842, 758, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 7.6 Hz, 2H), 7.41–7.35 (m, 2H), 7.29–7.22 (m, 1H), 6.98 (s, 1H), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.1 (d, *J* = 264.7 Hz), 136.9 (d, *J* = 4.7 Hz), 131.5 (d, *J* = 3.8 Hz), 128.8, 127.3, 126.6 (d, *J* = 4.7 Hz), 126.2 (d, *J* = 14.0 Hz), 124.7 (d, *J* = 24.9 Hz), –0.57; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.7 (s); GC-MS (EI, *m*/*z*, 70 eV) 250 (43, M^+), 235 (100), 205 (1), 191 (1), 171 (2), 158 (2), 133 (3), 118 (6), 95 (1), 77 (15); Anal. Calcd. for $C_{13}H_{15}FSSi$: C, 62.35; H, 6.04. Found: C, 62.38; H, 6.04.

(4-fluoro-5-phenylthiophen-2-yl)dimethyl(phenyl)silane (10gc)

Colorless oil; yield 70 % (93 % purity); IR (NaCl) 2958, 1665, 1601, 1574, 1555, 1494, 1428, 1362, 1252, 1111, 1035, 963, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.56 (m, 4H), 7.42–7.34 (m, 5H), 7.26 (d, *J* = 6.9 Hz, 1H), 6.99 (s, 1H), 0.6 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.1 (d, *J* = 264.7 Hz), 136.6, 134.8 (d, *J* = 4.7 Hz), 133.9, 131.4 (d, *J* = 3.9 Hz), 129.7, 128.8, 128.0, 127.5, 127.0 (d, *J* = 13.2 Hz), 126.7 (d, *J* = 4.6 Hz), 126.0 (d, *J* = 24.9 Hz), 0.84; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.5 (s); GC-MS (EI, *m*/*z*, 70 eV) 312 (51), 297 (100), 254 (2), 235 (3), 202 (5), 139 (10), 105 (3), 91 (4), 77 (4), 53 (1); HRMS (FAB, *m*/*z*) Calcd. for $C_{18}H_{17}FSSi$: 312.0804; Found: 312.0802.

(4-fluoro-5-phenylthiophen-2-yl)(methyl)diphenylsilane (10gd)

Colorless oil; yield 45 %; IR (NaCl) 3087, 1589, 1446, 1362, 1255, 1111, 1035, 963, 791, 728, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.56 (m, 6H), 7.47–7.33 (m, 8H), 7.29–7.25 (m, 1H), 7.01 (s, 1H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.1 (d, *J* = 264.7 Hz), 135.0, 134.7, 132.7 (d, *J* = 4.7 Hz), 131.3 (d, *J* = 3.9 Hz),

129.4 (d, *J* = 18.3 Hz), 128.3, 128.0, 127.9, 127.6 (d, *J* = 2.3 Hz), 127.3, 126.7 (d, *J* = 4.7 Hz), –2.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.3 (s); GC-MS (EI, *m*/*z*, 70 eV) 374 (64, M^+), 359 (100), 297 (10), 281 (5), 202 (8), 180 (6), 155 (3), 139 (7), 105 (5), 91 (2); Anal. Calcd. for $C_{23}H_{19}FSSi$: C, 73.75; H, 5.11. Found: C, 73.91; H, 4.97.

triethyl(4-fluoro-5-p-tolylthiophen-2-yl)silane (10ha)

Colorless oil; yield 81 %; IR (NaCl) 2956, 2911, 2876, 1571, 1556, 1509, 1455, 1358, 1189, 1018, 963, 828, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.96 (s, 1H), 2.36 (s, 3H), 1.01 (t, *J* = 8.0 Hz, 9H), 0.798 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.9 (d, *J* = 263.1 Hz), 137.2, 133.0 (d, *J* = 4.7 Hz), 154.9 (d, *J* = 263.1 Hz), 129.4, 128.7 (d, *J* = 3.9 Hz), 126.4 (d, *J* = 12.9 Hz), 125.4 (d, *J* = 24.9 Hz), 21.2, 7.3, 4.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –132.6 (s); GC-MS (EI, *m*/*z*, 70 eV) 306 (78, M^+), 277 (81), 249 (69), 221 (100), 205 (6), 171 (7), 139 (8), 125 (7), 111 (15); Anal. Calcd. for $C_{17}H_{23}FSSi$: C, 66.61; H, 7.56. Found: C, 66.82; H, 7.60.

[5-(4-chlorophenyl)-4-fluorothiophen-2-yl]triethylsilane (10ia)

Colorless oil; yield 89 %; IR (NaCl) 2956, 2876, 1568, 1553, 1492, 1358, 1238, 1095, 1018, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.97 (s, 1H), 1.02 (t, *J* = 7.8 Hz, 9H), 0.803 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.3 (d, *J* = 264.7 Hz), 134.3 (d, *J* = 4.7 Hz), 133.1 (d, *J* = 1.6 Hz), 130.0 (d, *J* = 3.9 Hz), 128.9, 127.7 (d, *J* = 5.4 Hz), 125.5 (d, *J* = 24.9 Hz), 125.0 (d, *J* = 13.2 Hz), 7.2, 4.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.1 (s); GC-MS (EI, *m*/*z*, 70 eV) 328 (28, $M^+[^{37}Cl]$), 326 (66, $M^+[^{35}Cl]$), 299 (33), 297 (79), 271 (28), 269 (67), 243

(41), 241 (100), 205 (7), 121 (14); Anal. Calcd. for $C_{16}H_{20}ClFSSi$: C, 58.78; H, 6.17. Found: C, 58.91; H, 6.17.

Triethyl[4-fluoro-5-(4-methoxyphenyl)thiophen-2-yl]silane (10ja)

Colorless oil; yield 77 %; IR (NaCl) 2955, 2910, 2876, 1610, 1558, 1509, 1440, 1358, 1293, 1249, 1181, 1039, 1018, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, *J* = 8.6 Hz, 2H), 6.95 (s, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.797 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.9, 154.4 (d, *J* = 262.4 Hz), 132.3 (d, *J* = 4.7 Hz), 127.9 (d, *J* = 4.6 Hz), 126.2 (d, *J* = 25.0 Hz), 125.4 (d, *J* = 2.5 Hz), 124.2 (d, *J* = 4.8 Hz), 114.2, 55.3, 7.2, 4.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –133.7 (s); GC-MS (EI, *m*/*z*, 70 eV) 322 (97, M^+), 293 (76), 265 (69), 237 (100), 222 (6), 173 (4), 145 (5), 133 (10), 119 (25), 77 (4); Anal. Calcd. for $C_{17}H_{23}FOSSi$: C, 63.31; H, 7.19. Found: C, 63.48; H, 7.13.

[5-(2-chlorophenyl)-4-fluorothiophen-2-yl]triethylsilane (10ka)

Colorless oil; yield 77 %; IR (NaCl) 2956, 2876, 1567, 1444, 1360, 1238, 1069, 1017, 964, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.40 (m, 2H), 7.30–7.25 (m, 2H), 6.98 (s, 1H), 1.03 (t, *J* = 8.0 Hz, 9H), 0.817 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.6 (d, *J* = 264.7 Hz), 136.1 (d, *J* = 4.6 Hz), 133.6, 132.2 (d, *J* = 3.1 Hz), 130.1, 129.9 (d, *J* = 3.1 Hz), 129.3, 126.6, 123.9 (d, *J* = 24.1 Hz), 122.9 (d, *J* = 16.3 Hz), 7.3, 4.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –129.3 (s); GC-MS (EI, *m*/*z*, 70 eV) 328 (22, $M^+[^{37}Cl]$), 326 (51, $M^+[^{35}Cl]$), 299 (32), 297 (79), 271 (26), 269 (62), 243 (41), 241 (100), 158 (10), 121 (22); Anal. Calcd. for $C_{16}H_{20}ClFSSi$: C, 58.78; H, 6.17. Found: C, 58.87; H, 6.03.

3-Fluoro-2-phenylthiophene (10ge)

Colorless oil; yield 29 %; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.59 (m, 1H), 7.41–7.37 (m, 1H), 7.35–7.30 (m, 1H), 7.12 (dd, *J* = 5.5, 3.9 Hz, 1H), 6.87 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.9 (d, *J* = 260.8 Hz), 134.4, 131.2 (d, *J* = 3.9 Hz), 128.8, 127.4, 126.7 (d, *J* = 4.7 Hz), 122.0 (d, *J* = 10.1 Hz), 118.7 (d, *J* = 27.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 131.6 (d, *J* = 2.8 Hz) (s); GC-MS (EI, *m*/*z*, 70 eV) 178 (100, M^+), 158 (4), 146 (10), 133 (22), 126 (2), 107 (4), 89 (5), 77 (2), 69 (2), 51 (1).

2.5. References

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(9) The structure of **9g** was identified by ^{1}H and ^{19}F NMR spectra and GC-MS [*m*/*z* = 312 (6, M^{+})]. The methine proton signal appeared at 5.82 (s) and the vinylic proton signal did at 4.89 (dd, *J* = 20.8, 17.4 Hz), respectively. Two *gem*-fluorine signals appeared at –85.0 (dd, *J* = 254.8, 20.8 Hz) and –86.1 (dd, *J* = 254.8, 17.4 Hz), respectively. This 4,4-difluoro-3,4-dihydrothiophene **9g** was easily transformed into **10ga** during silica gel column chromatographic purification.

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Chapter four

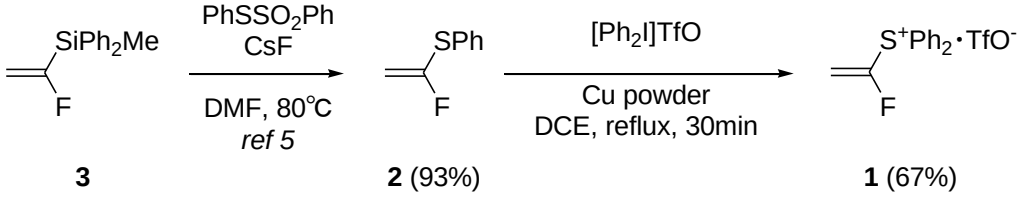
Synthesis of mono-Fluorinated Functionalized Cyclopropanes and Aziridines using the (1-Fluorovinyl)diphenylsulfonium Salt

4.1. Introduction

β-(Trifluoromethyl)vinyl sulfonium salt is a powerful building block for the synthesis of trifluoromethylated compounds such as cyclopropanes, aziridines, and α-(trifluoromethyl)vinyl molecules.[1] Among them, trifluoromethylated cyclopropanes are attractive products due to their high reactivity. In a similar sense, mono-fluorinated cyclopropanes have drawn much attention due to their wide utility as precursors of medicinal materials.[2] There are a large number of examples using addition reactions of fluorocarbenes to olefins or carbenes to fluoroolefins in the literature.[3] On the other hand, the synthesis of such molecules using annulation reactions is scarce.[2a,4] The author considered that these molecules may be accessible from appropriate active methylene compounds and the monofluorinated vinyl sulfonium salt under mild conditions. To the best of my knowledge, there is no report so far concerning the mono-fluorinated vinyl sulfonium salt. The author discloses the first preparation of α-fluorovinyl sulfonium salt and its synthetic applications.

4.2. Results and discussion

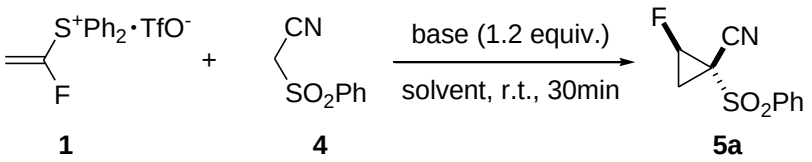
The author planned the synthetic route of **1** is shown in Scheme 1. Because our group has already reported the facile preparation of the requisite α-fluorovinyl phenyl sulfide **2** from (1-fluorovinyl)methyldiphenylsilane **3**.[5,6] According to the reported procedure, the author next examined the quarternization of **2** with diphenyliodonium triflate in the presence of a catalytic amount of CuCl(I).[1] As the author expected, the reaction proceeded giving the desired salt **1**. To my disappointment, the reaction mixture generally turned black during the progress of quarternization. To make matters worse, the resulting contaminated reaction mixtures required tedious purification steps. The extra process caused decrease of the yield. In order to avoid this unfavorable color-change, the author investigated more preferable reaction conditions. After many unsuccessful attempts, the author reached the acceptable reaction conditions. Thus, when the reaction was carried out using **2** (0.95 equiv.) and diphenyliodonium triflate (1.0 equiv.) in the presence of Cu powder (5.0 equiv.) instead of CuCl(I) in dichloroethane (DCE) under reflux conditions for 30 min, the author obtained **1** as a white solid in 67 % yield after purification by silica gel column chromatography. The salt **1** is also free-flowing, shelf-stable, and easy to handle, as is often the case with vinyl sulfonium triflates.



Scheme 1. Synthesis of (1-fluorovinyl)sulfonium salt **1**

With the practical procedure of **1** in hand, the author examined the reactivity of **1**. The model reaction was tested using **1** (1.2 equiv.) and 2-(phenylsulfonyl)acetonitrile **4** (1.0 equiv.) at room temperature in the presence of DBU (1.2 equiv.) as a base in DMSO.[7] The expected cyclization reaction proceeded with ease to give the desired mono-fluorinated cyclopropane derivative **5a** as a mixture of diastereomers (92/8) in 89 % combined yield. Unfortunately, this diasteromeric mixture could not be easily separated into its components. To improve both chemical yield and diastereoselectivity, the author optimized the reaction conditions relative to the parameters such as solvent and base. The results are shown in Table 1. Most reaction conditions tested still keep the yield within an acceptable range with high diastereoselectivity. Taking both yield and diastereoselectivity into consideration in Table 1, the author determined that the reaction conditions of entry 2 were best.

Table 1. Optimization of reaction conditions[a]



1 **4** **5a**

entry	solvent	base	yield[b] (%)	dr[c]
1	DMSO	DBU	89	92/8
2	CH_3CN	DBU	93	95/5
3	DCM	DBU	76	96/4
4	DMSO/THF (1/1)	DBU	89	93/7
5	THF	DBU	91	95/5
6	DMSO	NaH	87	92/8
7	DMSO	*t*BuOK	39	92/8
8	DMSO	K_2CO_3[d]	69	93/7
9	AcOEt	K_2CO_3[d]	89	96/4

[a] The reaction of **1** (1.2 equiv.) with **4** (1.0 equiv.) was carried out. [b] Isolated yield. [c] Determined by ^1H or ^{19}F NMR. [d] K_2CO_3 (3.0 equiv.) was used.

As far as the stereochemistry of **5a** is concerned, the author performed the X-ray analysis of **5a**. Actually, the major isomer **5a** was confirmed by X-ray analysis (Figure 1).[8] The ORTEP drawing of **5a** revealed that there was a cis-relationship between the vicinal fluoro and cyano groups.

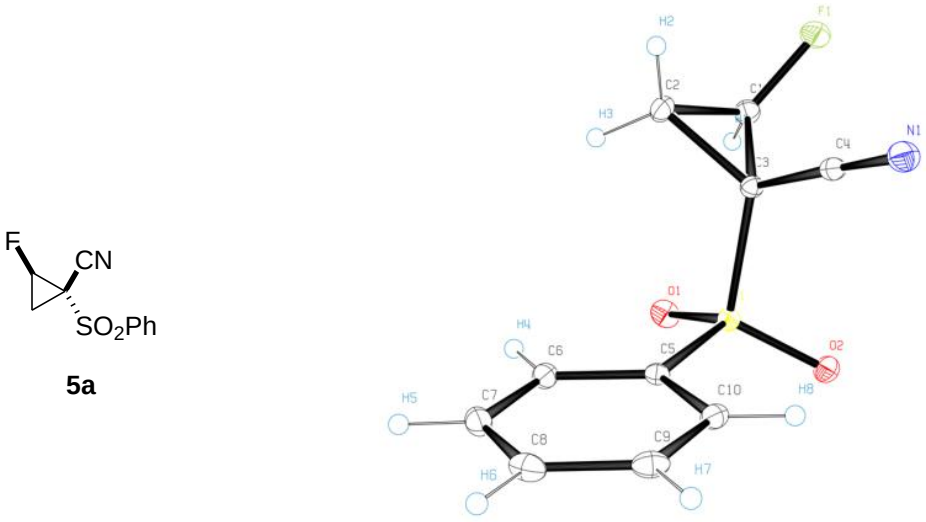
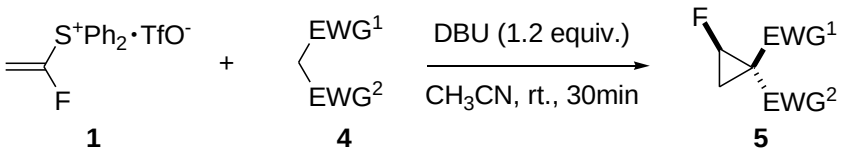


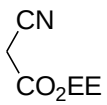
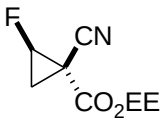
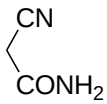
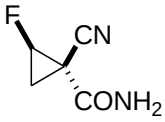
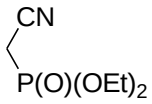
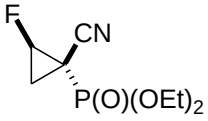
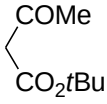
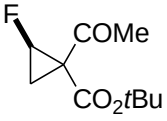
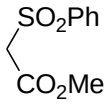
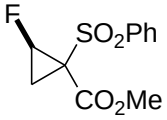
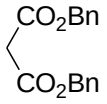
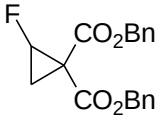
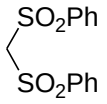
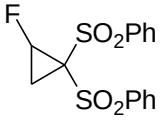
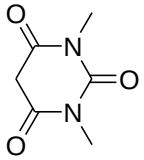
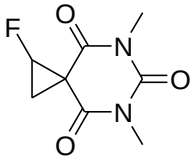
Figure 1. Xray structure of **5a**

Having found the optimal conditions, the author explored the substrate scope of this cyclization protocol (Table 2). A variety of active methylene compounds bearing a wide range of electron-withdrawing groups took part in this reaction, affording the corresponding mono-fluorinated cyclopropane derivatives **5** in good to excellent yields. Reaction substrates having highly polar amide or imido groups underwent smooth cyclization (entries 3, 8). Among the products, the product **5d** (entry 4) was more volatile than other products. That is the reason why the product **5d** was obtained in slightly low yield. Although the author made considerable effort (prolonged reaction time, elevated temperature, and increased amount of the base) for the reaction of entries 5–7, complete reactions were not achieved. These observations also supported slightly decreased yields. It is noteworthy that all active methylene compounds containing a cyano group gave high diastereoselectivity of the product (entries 1–4). The stereochemistry of all these major products except for **5a** was tentatively assigned by

analogy as shown in Table 2 on the basis of ^{1}H and ^{19}F NMR data in comparison with that of **5a**. When the author conducted the reaction of tert-butyl acetoacetate (entry 5) containing a ketone functionality in the cyclization reaction, obtained was a small amount of an inseparable unidentified by-product in addition to two diastereomers of the corresponding monofluorinated cyclopropanes **5e**.

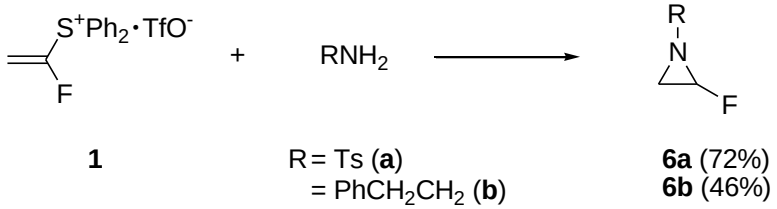
Table 2. Substrate scope[a]



entry	substrate	product[b]	**5**	yield (%)[c]	dr[d]
1			**5b**	98	91/9
2[e]			**5c**	79	98/2
3			**5d**	70	91/9
4			**5e**	79 (86)[f]	72/28
5			**5f**	83 (94)	50/50
6			**5g**	77 (91)	-
7			**5h**	93	-
8			**5i**	96	-

[a] The reaction of **1** (1.2 equiv.) with **4** (1.0 equiv.) was carried out. [b] Major stereoisomer is shown. [c] Isolated yield and The yield based on the consumed starting material in parentheses. [d] Determined by ^{1}H or ^{19}F NMR. [e] EE = ethoxyethyl. [f] Percent yield is including a small amount of an unidentified product.

The author tried to appeal the utility of the salt **1**. The next target molecule was selected to the corresponding aziridine. The cyclization reaction of **1** with a primary amine was expected to produce mono-fluorinated aziridine (Scheme 2).[9] Referring to our previous procedure for the synthesis 2-trifluoromethyl-*N*-Ts-aziridine,[10] the reaction of **1** and *p*-toluenesulfonamide ($TsNH_2$) was conducted in the presence of NaH in THF. As the result, the reaction proceeded affording the corresponding 2-fluoro-*N*-Ts-aziridine **6a** in 72 % yield as a white solid. This is the first example of the preparation of **6a**. The author believes that this free-flowing and easy-handling aziridine **6a** should come to be a versatile mono-fluorinated building block of nitrogen-containing biologically active molecules. In addition to $TsNH_2$, β-phenethylamine as a primary alkyl amine participated in this aziridination reaction. Thus, the reaction of **1** and β-phenethylamine was carried out in the presence of *t*$BuNH_2$ in DMSO at room temperature, giving the corresponding 2-trifluoromethyl-*N*-β-phenethyl-aziridine **6b** in 48 % yield.[9a]



Scheme 2. Synthesis of 2-fluoroaziridine **6**

4.3. Conclusion

In summary, the author has successfully developed a new mono-fluorinated vinyl

sulfonium salt **1** in one step and demonstrated its high performance for the synthesis of mono-fluorinated cyclopropanes and aziridines under mild conditions.

4.4. Experimental

4.4.1. General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured in $CDCl_3$ and/or DMSO-d_6 solutions, unless otherwise stated. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^{1}H NMR and ^{13}C NMR spectra. On the other hand, chemical shifts were given by δ relative to that of $CFCl_3$ for ^{19}F NMR spectra using an internal $CF_3C_6H_5$ (benzotrifluoride) or C_6F_6. Infrared (IR) spectra are reported in cm^{-1}. Melting points are uncorrected.

4.4.2. Preparation of 1

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock was charged with (1-fluorovinyl)phenylsulfide **3** (82.0 mg, 0.532 mmol, 1.0 equiv.) in 1 mL of 1,2-dichloroethane (CH_2ClCH_2Cl) under argon. To this solution was added diphenyliodonium triflate (212.0 mg, 0.506 mmol, 0.95 equiv.) and Cu powder (174.0 mg, 2.67 mmol, 5.0 equiv.). The reaction mixture was refluxed for 30 min. After cooling to room temperature, the mixture was directly purified by silica gel chromatography (CH_2Cl_2 then CH_2Cl_2/acetone = 10/1–2/1) to give the desired product **1** as a white solid (129.0 mg, 67 %).

4.4.3. Preparation of 5a

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock was charged with phenylsulfonylacetonitrile **4a** (39.9 mg, 0.22 mmol. 1.0 equiv.) and DBU (39 μL, 0.261 mmol, 1.2 equiv.) in acetonitrile (1 mL) under argon. After stirring for 5 min, to this solution was added the salt **1** (99.4 mg, 0.261 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with hexane/AcOEt = 1/1. The extraction was repeated twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt = 5/1–1/1) to give the desired product **5a** as a white solid (46.0 mg, 93 %).

4.4.4. Preparation of 6a

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock was charged with *p*-toluenesulfonamide (33.0 mg, 0.193 mmol, 1.0 equiv.) in 1 mL of THF under argon. To this solution was added NaH (67.2 % oil dispersion, 35.0 mg, 0.234 mmol, 1.2 equiv.) and the mixture was stirred for 15 min. To the resulting solution was added the salt **1** (78.0 mg, 0.205 mmol, 1.05 equiv.). After the reaction mixture was stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the organic layer was separated, additional extraction with hexane/AcOEt = 3/1 was repeated twice. The combined organic solution was dried over Na_2SO_4. The solution was concentrated in vacuo and the residual oil was purified by silica gel chromatography (hexane/AcOEt =

3/1) to give the desired product **6a** as a white solid (29.8 mg, 72 %).

4.4.5. Preparation of 6b

A 25 mL two-necked flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock was charged with β-phenethylamine (44.1 μL, 0.350 mmol, 1.0 equiv.) in 1 mL of DMSO under argon. To this solution was added *t*BuNH$_2$ (110 μL, 1.05 mmol, 3.0 equiv.) and the salt **1** (146 mg, 0.385 mmol, 1.1 equiv.). After the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with water and extracted with ether. The combined organic solution was dried over Na_2SO_4. The solution was concentrated in vacuo and the residual oil was purified by silica gel chromatography (hexane/ether = 2/1) to give the desired product **6b** as a colorless oil (27.1 mg, 48 %).

4.4.6. Data of products (1, 5a–5i, 6a)

(1-Fluorovinyl)-diphenyl-sulfonium trifluoromethanesulfonate (1)

white solid; yield 67 %; mp: 71.0–72.0 ℃; IR (KBr) 3128, 3047, 2996, 1645, 1579, 1478, 1452, 1265, 1143, 1028, 944, 749, 683, 637, 572, 548, 517, 486 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 8.0 Hz, 4H), 7.83 (t, *J* = 7.3 Hz, 2H), 7.76–7.71 (m, 4H), 6.60 (dd, *J* = 42.7, 6.0 Hz, 1H), 6.14 (dd, *J* = 10.9, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 146.0 (d, *J* = 315.3 Hz), 135.2, 131.6, 130.8, 121.2, 120.5 (q, *J* = 320.7 Hz), 114.9 (d, *J* = 7.8 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –79.6 (s, 3F) –104.7 (dd, *J* = 42.7, 10.9 Hz); Anal. Calcd. for $C_{15}H_{12}F_4O_3S_2$: C, 47.36, H, 3.18; Found: C, 47.34, H, 3.14.

2-Fluoro-1-(phenylsulfonyl)cyclopropanecarbonitrile (5a)

White solid; yield 93 %; dr: 95/5; mp: 99.5–110.1 ℃; IR (ATR) 3111, 3021, 2245, 1583, 1450, 1422, 1327, 1306, 1180, 1155, 856, 723, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 2H), 5.26 (dt, *J* = 60.8, 5.5 Hz, 1H), 2.39–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.2, 135.5, 129.9, 128.8, 111.9 (d, *J* = 3.9 Hz), 72.8 (d, *J* = 248.3 Hz), 37.0 (d, *J* = 10.1 Hz), 21.5 (d, *J* = 9.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –207.2 (ddd, *J* = 60.8, 19.1, 13.2 Hz); GC-MS (EI, *m*/*z*, 70 eV) 225 (53, M^+), 160 (4), 141 (26), 125 (18), 109 (4), 97 (4), 77 (100), 73 (9), 65 (2), 51 (25); Anal. Calcd. for $C_{10}H_8FNO_2S$: C, 53.32; H, 3.58; N, 6.22. Found: C, 53.36; H, 3.38; N, 6.21.

2-Ethoxyethyl 1-cyano-2-fluorocyclopropanecarboxylate (5b)

Colorless oil; yield 98 %; dr: 91/9; IR (ATR) 2978, 2873, 2253, 1737, 1377, 1302, 1269, 1121, 882, 859 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.02 (ddd, *J* = 62.0, 5.8, 4.5 Hz, 1H), 4.39–4.31 (m, 2H), 3.71–3.66 (m, 2H), 3.56 (q, *J* = 6.9 Hz, 2H), 2.14 (ddd, *J* = 21.3, 7.4, 4.3 Hz, 1H), 2.03 (ddd, *J* = 15.5, 7.4, 5.8 Hz, 1H), 1.22 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.3, 113.8 (d, *J* = 3.8 Hz), 75.1 (d, *J* = 244.5 Hz), 67.5, 66.7, 66.3, 23.6 (d, *J* = 7.8 Hz), 19.7 (d, *J* = 10.9 Hz), 15.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –204.7 (ddd, *J* = 62.0, 21.3, 15.5 Hz); GC-MS (EI, *m*/*z*, 70 eV) 172 , (1, M^+–Et), 156 (47), 142 (5), 129 (8), 112 (67), 98 (4), 84 (31), 72 (25), 59 (100).

1-Cyano-2-fluorocyclopropanecarboxamide (5c)

White solid; yield 79 %; dr: 98/2; mp: 120 °C (sublimation); IR (KBr) 3407, 3211, 3124, 2249, 1667, 1436, 1402, 1282, 1203, 1146, 1068, 1053, 1030, 876, 752, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.43 (bs, 1H), 5.77 (bs, 1H), 5.01 (ddd, *J* = 62.4, 5.1, 4.7 Hz,

1H), 2.20–2.00 (m, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 164.8, 116.4 (d, J = 4.7 Hz), 75.2 (d, J = 237.4 Hz), 21.9 (d, J = 8.5 Hz), 20.0 (d, J = 9.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 206.5 (ddd, J = 62.4, 22.7, 16.7 Hz); Anal. Calcd. for $C_5H_5FN_2O$: C, 46.88; H, 3.93; N, 21.87. Found: C, 47.01; H, 3.84; N, 21.84.

Diethyl 1-cyano-2-fluorocyclopropylphosphonate (5d)

Colorless oil; yield 70 %; dr: 91/9; IR (ATR) 2987, 2243, 1443, 1367, 1258, 1189, 1012, 860, 800, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.04, (dddd, J = 62.0, 9.4, 5.6, 3.9 Hz, 1H), 4.33–4.18 (m, 4H), 2.08–1.92 (m, 1H), 1.92–1.78 (m, 1H), 1.44 (t, J = 6.9 Hz, 3H), 1.41 (t, J = 6.9 Hz 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 114.3 (d, J = 6.2 Hz), 72.3 (d, J = 242.9 Hz), 64.3 (t, J = 6.2 Hz), 19.4 (dd, J = 10.2, 3.8 Hz), 16.2 (d, J = 3.1 Hz), 16.3 (d, J = 2.3 Hz), 11.3 (dd, J = 193.0, 10.1 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 208.8 (dddd, J = 62.0, 20.3, 13.1, 3.6 Hz); GC-MS (EI, m/z, 70 eV) 206 (2, M^+–Me), 193 (5), 178 (2), 165 (100), 145 (49), 117 (7), 109 (4), 107 (5), 81 (14), 65 (8).

tert-Butyl 1-acetyl-2-fluorocyclopropanecarboxylate (5e)

yield 79 %; dr: 72/28

5ea (major, less polar); Colorless oil; IR (NaCl) 2981, 1725, 1699, 1245, 1369, 1325, 1262, 1215, 1174, 1146, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.94 (dm, J = 65.1 Hz, 1H), 2.43 (s, 3H), 2.14 (dm, J = 22.1 Hz, 1H), 1.65–1.45 (m, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 201.3, 165.0, 82.9, 77.2 (d, J = 237.4 Hz) , 42.4, 27.9, 22.3 (d, J = 7.8 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –212.6 (ddd, J = 65.1, 22.1, 14.4 Hz). GC-MS (EI, m/z, 70 eV) 146 (51), 129 (57, M^+–OtBu), 141 (26), 101 (2), 87 (28), 81 (11), 70 (2), 57 (100).

5eb (minor, more polar); Colorless oil; IR (NaCl) 2980, 2935, 1712, 1425, 1370, 1302, 1168, 1120, 1071cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.99 (dm, *J* = 62.6 Hz, 1H), 2.42 (s, 3H), 2.18 (dm, *J* = 22.6 Hz), 1.55–1.45 (m, 1H) 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 83.0, 75.5 (d, *J* = 232.8 Hz), 30.4, 28.0, 18.4 (d, *J* = 8.8 Hz), three carbon was lost; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –215.2 (ddd, *J* = 62.6, 22.6, 13.1 Hz). GC-MS (EI, *m*/*z*, 70 eV) 146 (37), 129 (39, M^+–O*t*Bu), 87 (20), 81 (7), 57 (100).

Methyl 2-fluoro-1-(phenylsulfonyl)cyclopropanecarboxylate (5f)

yield 83 %; dr: 50/50

5fa (less polar); White solid; mp: 74.0–75.0 °C; IR (KBr) 3131, 3073, 3042, 2964, 1746, 1450, 309, 1228, 1162, 1161, 1121, 1073, 1013, 960, 885, 819, 735, 683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–7.94 (m, 2H), 7.71–7.67 (m, 1H), 7.62–7.56 (m, 2H), 5.28 (ddd, *J* = 63.8, 7.0, 4.7 Hz, 1H), 3.73 (s, 3H), 2.51 (ddd, *J* = 20.2, 7.9, 4.7 Hz, 1H), 2.32 (ddd, *J* = 12.9, 7.9, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 162.5, 138.9, 134.2, 129.2, 128.9, 74.7 (d, *J* = 245.2 Hz), 53.2, 49.4 (d, *J* = 10.9 Hz), 19.7 (d, *J* = 9.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –214.1 (ddd, *J* = 63.8, 20.2, 12.9 Hz); GC-MS (EI, *m*/*z*, 70 eV) 258 (14, M^+), 227 (22), 194 (8), 162 (28), 141 (22), 134 (25), 125 (24), 117 (33), 87 (12), 77 (100), 63 (29), 59 (15), 51 (31).

5fb (more polar); Colorless oil (81 % pure); IR (NaCl) 3070, 2958, 1743, 1448, 1329, 1285, 1170, 1135, 1082, 952, 895, 812, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.70–7.61 (m, 1H), 7.61–7.54 (m, 2H), 4.89 (ddd, *J* = 64.2, 6.3, 4.9 Hz, 1H), 3.67 (s, 3H), 2.88 (ddd, *J* = 21.5, 7.6, 4.9 Hz, 1H), 2.16 (ddd, *J* = 13.2, 7.6, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.1, 139.5, 134.3, 133.9, 128.7, 75.8 (d, *J* = 247.6 Hz), 53.1, 48.0 (d, *J* = 11.6 Hz), 19.75 (d, *J* = 8.5 Hz); ^{19}F NMR ($CDCl_3$, 376

MHz) δ –211.7 (ddd, *J* = 64.2, 21.5, 13.2 Hz); GC-MS (EI, *m*/*z*, 70 eV) 258 (42, M^+), 227 (16), 194 (5), 162 (14), 141 (22), 134 (24), 125 (32), 117 (19), 87 (8), 77 (100), 63 (19), 59 (13), 51 (30).

Dibenzyl 2-fluorocyclopropane-1,1-dicarboxylate (5g)

Colorless oil; yield 77 %; IR (ATR) 3035, 1723, 1311, 1277, 1210, 1118, 1073, 1025, 903, 734, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.21 (m, 10H), 5.29–4.99 (m, 5H), 2.23 (ddd, *J* = 22.3, 7.2, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.6 , 164.3 (d, *J* = 3.1 Hz), 128.6 , 128.5, 128.4, 128.3, 128.13, 128.07, 75.1 (d, *J* = 235.9 Hz), 67.9, 67.5, 34.4 (d, *J* = 12.5 Hz), 20.3 (d, *J* = 9.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 213.1 (ddd, *J* = 64.4, 22.3, 14,3 Hz); GC-MS (EI, *m*/*z*, 70 eV) 237 (7, M^+–Bn), 219 (5), 184 (5), 180 (5), 171 (6), 131 (30), 107 (42), 91 (100), 65 (12).

1-(2-Fluoro-1-(phenylsulfonyl)cyclopropylsulfonyl)benzene (5h)

White solid; yield 93 %; mp: 87.0–88.2 °C; IR (ATR) 3107, 3072, 1583, 1449, 1419, 1330, 1236, 1175, 1150, 1078, 979, 883, 801, 751, 729, 715, 685, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.04 (m, 2H), 8.01–7.96 (m, 2H), 7.76–7.67 (m, 2H), 7.62–7.54 (m, 4H), 5.51 (ddd, *J* = 64.2, 6.8, 4.7 Hz, 1H), 2.91 (ddd, *J* = 20.1, 8.6, 4.7 Hz, 1H), 2.07 (ddd, *J* = 12.5, 8.6, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.7, 137.6, 134.7 , 134.5, 123.0, 129.8, 129.7, 129.0, 128.7, 73.5 (d, *J* = 248.3 Hz), 61.0 (d, *J* = 10.9 Hz), 20.0 (d, *J* = 10.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 214.6 (ddd, *J* = 64.2, 20.1, 12.5 Hz); GC-MS (EI, *m*/*z*, 70 eV) 232 (5), 167 (1), 141(27), 139 (7), 125 (11), 107 (65), 91 (47), 77 (100), 51 (26).

1-Fluoro-5,7-dimethyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (5i)

Whit solid; yield 96 %; mp: 88.5–90.2 °C; IR (KBr) 3114, 3073, 2963, 2533, 1746, 1681, 1470, 1385, 1293, 1176, 1131, 1070, 1038, 852, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.05 (ddd, *J* = 64.4, 6.1, 5.2 Hz, 1H), 3.37 (s, 3H), 3.33 (s, 3H), 2.70 (ddd, *J* = 21.5, 6.1, 5.2 Hz, 1H), 2.29 (dt, *J* = 14.8, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.4, 163.1, 151.5, 81.5 (d, *J* = 254.5 Hz), 33.2 (d, *J* = 10.1 Hz), 28.8, 28.6, 24.5 (d, *J* = 7.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 206.3 (ddd, *J* = 64.4, 21.5, 14.8 Hz); Anal. Calcd. for $C_8H_9FN_2O_3$: C, 48.00; H, 4.53; N, 14.00. Found: C, 48.09; H, 4.49; N, 13.90.

2-Fluoro-N-tosylaziridine (6a)

Whit solid; yield 71 %; mp: 56.9–57.5 ℃; IR (KBr) 3077, 1595, 1448, 1381, 1324, 1254, 1168, 1124, 1095, 1061, 974, 882, 812, 731, 674, 573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 5.40 (ddd, *J* = 72.2, 2.4, 2.2 Hz, 1H), 2.80–2.75 (m, 1H), 2.71–2.68 (m, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 145.3, 134.3, 129.9, 127.9, 76.7 (d, *J* = 255.3 Hz), 34.0 (d, *J* = 13.3 Hz), 21.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –178.3 (d, *J* = 72.2 Hz); GC-MS (EI, *m*/*z*, 70 eV) 215 (2 M^+), 184 (66), 155 (91), 139 (2), 107 (2), 91 (100), 77 (3), 65 (23); Anal. Calcd. for $C_9H_{10}FNO_2S$: C, 50.22; H, 4.68; N, 6.51. Found: C, 50.39; H, 4.73; N, 6.50.

4.5. References

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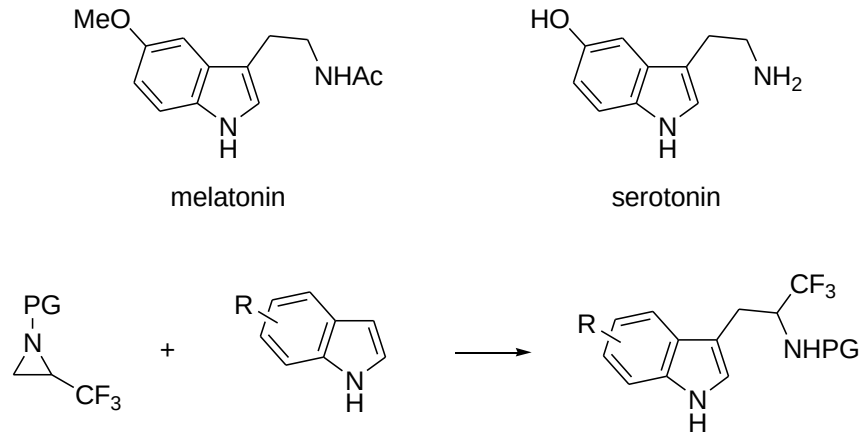
Chapter five

Diethylzinc-Promoted Synthesis of CF_3-containing Tryptamine Analogues from Indoles and 2-CF_3-N-Ts-Aziridine

5.1. Introduction

A component of several classes of bioactive natural compounds includes the indole framework.[1] On the other hand, introduction of β-aminoethyl group at the C-3 position of the indole ring brings us to the tryptamine family, which includes melatonin and serotonin.[2] Considering the promising effect of the existence of fluorine atom in bioactive molecules, introduction of a trifluoromethyl group into the indole side chain may enhance their highly beneficial effects for medical treatment. The simple and effective modification of bioactive tryptamines remains an important task in modern organic chemistry. The author's literature research revealed that there are only a few reports on the modification of tryptamines containing a trifluoromethyl group (CF_3) in the side chain. Among these, there are few reports about β-CF_3-tryptamine.[3] As mentioned above, fluoro substituents are powerful modifiers of the chemical and biological properties of organic compounds. There are many related reports found in pharmaceuticals and agrochemicals.[4] Therefore, it is an important objective to develop a facile method for the synthesis of a trifluoromethylated tryptamine. From a synthetic viewpoint, the most direct method seems to synthesize the tryptamine from an indole and a 2-(trifluoromethyl)aziridine derivative (Scheme 1).[5]



Scheme 1. Structures of tryptamines

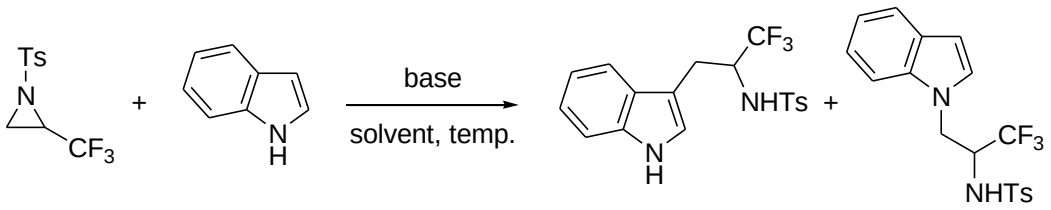
5.2. Results and discussion

There are many reports using this methodology with fluorine-free aziridines and indoles under several Lewis acidic conditions to give the corresponding ring-opening product.[6] However, the above fluorine-free aziridines almost always possess an electron-donating group in the aziridine ring. At any rate, our preliminary attempts with indole and 2-CF_3-*N*-Ts-aziridine **1** in the presence of $AgSbF_6$ or $BF_3{\cdot}OEt_2$ resulted in the quantitative recovery of both starting materials. These finding suggested the negative effect of the existence of electron-withdrawing group retarded the ring-opening reaction in our case. Then the author turned my attention to the execution of the reaction under Lewis basic conditions. Unlike Lewis acidic conditions, reports of the reaction under Lewis basic conditions are few.[3c,7] One of the main shortcomings of this transformation appears to be low product yields.

During the course of our group efforts to explore the synthetic utilization of

2-CF_3-*N*-Ts-aziridine **1**,[8] our group have recently reported the regioselective ring-opening reaction of **1** with some nucleophiles under basic conditions.[9] In this study, we carried out the reaction of **1** with an indole in the presence of *t*BuOK as a base under basic conditions to obtain the corresponding N-1 adduct of the indole in excellent yield with complete regioselectivity (Table 1, entry 10). The author got the hint of the solution of own problem. If this ring-opening reaction proceeds smoothly at the C-3 position of the indole, it could provide a solution for the synthesis of CF_3-containing tryptamine analogues. The author considered that the difference between N-alkylation and C–alkylation must be attributed to the HSAB theory. The author discloses the first diethylzinc-promoted direct C-3 alkylation of indoles with **1** under basic conditions.

Table 1. Optimization of the reaction conditions[a]



1 **2a** **3a** **4a**

entry	**2a** (equiv.)	base (equiv.)	solvent	temp. (℃)	time (h)	yield (%)[b] **3a**	**4a**
1	2.0	none	toluene	100	48	NR[c]	
2	2.0	Et_2Zn (2.0)	toluene	25	24	NR[c]	
3	2.0	Et_2Zn (2.0)	toluene	100	24	quant	0
4	1.3	Et_2Zn (1.3)	toluene	100	17	quant[d]	0
5	1.3	Et_2Zn (1.3)	1,4-dioxane	100	24	quant	0
6	1.3	Et_2Zn (1.3)	toluene	80	72	93	0
7	1.3	Et_2Zn (0.6)	toluene	100	72	52	0
8	1.3	Et_2Zn (0.2)	toluene	100	72	trace	0
9	1.1	NaH (1.1)	DMSO	25	1	0	quant
10[e]	1.1	*t*BuOK (1.1)	DMSO	25	1	0	quant[f]

[a] **1** (0.23 mmol, 1.0 equiv.) and Et_2Zn (1.06 M in hexane) were used. [b] GC-MS yield. [c] No reaction. [d] 99 % isolated yield. [e] See Ref. 9. [f] 98 % isolated yield.

The author selected indole **2a** in order to examine the diethylzinc-promoted ring-opening model reaction.[10] When two equivalents of **2a** and diethylzinc were treated with one equivalent of **1** in toluene at 25 °C, no reaction took place, even after 24 h (entry 2). Then the author tried this reaction under more harsh conditions. Fortunately, when the same reaction was just heated to 100 °C, the desired ring-opening

product **3a** was obtained with excellent regioselsectivity in quantitative yield (entry 3). This is the first successful example of the ring-opening reaction of aziridine with an indole promoted by a zinc reagent. Encouraged by this promising result, the author continued to optimize the reaction conditions. Even if was reduced the amount of indole and diethylzinc down to 1.3 equivalents from 2.0 equivalents, no detrimental effects were observed (entry 4). In addition to toluene solvent, the use of 1,4-dioxane essentially tolerated the reaction (entry 5). Lowering the reaction temperature required prolonged reaction times (entry 6). Decreasing the amount of diethlyzinc (0.6 equiv.) relative to the indole caused an incomplete reaction (entry 7). This finding suggested that the stoichiometric amount of diethylzinc is necessary for the successful reaction and this reaction did not proceed with a catalytic amount of diethylzinc. The use of a different base (NaH) gave a complete reversal of the regioselectivity, yielding **4a** in quanititative yield (entry 9). The author produced the single crystals of adduct **3a** suitable for X-ray crystallographic analysis. The ORTEP drawing of **3a** is shown in Figure 1.[11] The author obtained unambiguous proof of the regiochemistry of the C-3 substitution of the indole.

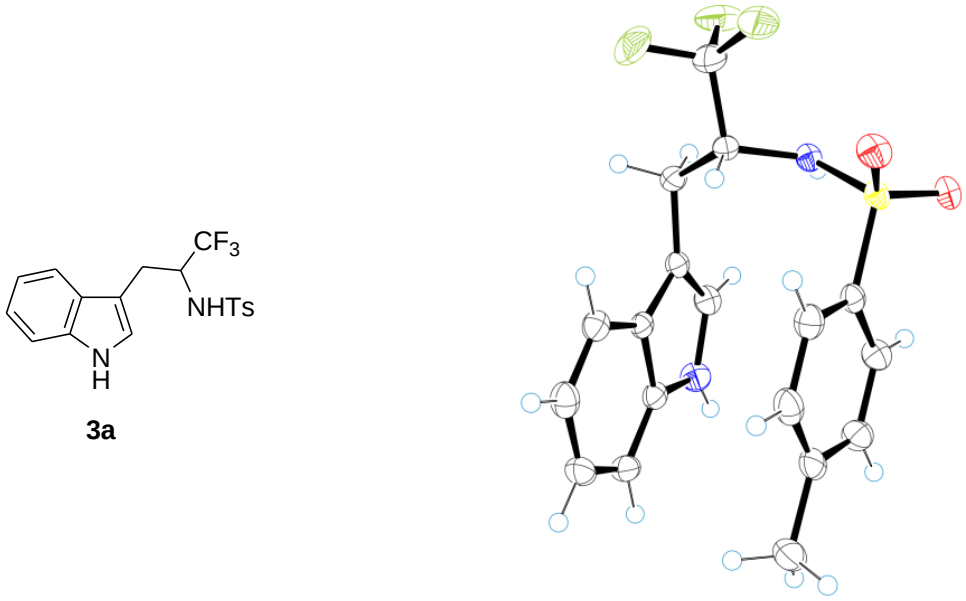
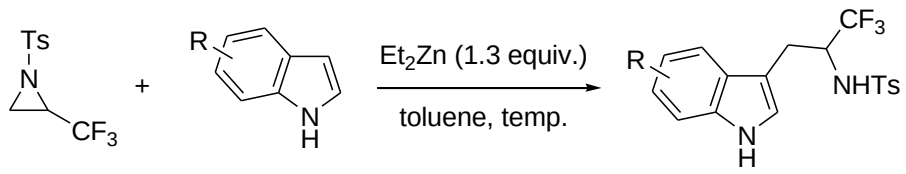


Figure 1. ORTEP drawing of the adduct **3a** with thermal ellipsoids shown at 50% probability level

Having finished the optimal reaction conditions for the synthesis of CF_3-tryptamine **3a** (Table 1, entry 4), the author subsequently explored the substrate scope of this transformation with respect to commercially available indoles and their derivatives. Table 2 shows that most indoles took part in this nucleophilic substitution reaction at C3 position to give the corresponding CF_3-trypramines in excellent yields and complete regioselectivity. Electron-donating (OMe, OBn, OTBDMS, Ph, Me) and electron-withdrawing (Br, CO_2Me, CN) substituents at the C-5, C-4, and C-2 positions of the indoles were compatible with this transformation. Among them, 5-cyanoindole was a reluctant nucleophile, its reaction resulted in an incomplete reaction along with the recovery of unreacted aziridine **1** under the same reaction conditions. To overcome this difficulty, the author used a larger amount of indole (2.3 equiv.) and diethylzinc (2.3 equiv.) in chlorobenzene/THF = 10/1 at 130 °C for 54 h; however, the satisfactory

conversion of **1** did not occur (entry 6). Unfortunately, when the author employed 4-hydroxyindole for this reaction, no ring-opening reaction occurred, and both starting materials were recovered although the author used twice the amount of diethylzinc (2.6 equiv.). At the present time, the reason for this unsuccessful reaction is unclear. Moreover, it is noteworthy that N-methyl indole did not participate in this reaction; the free NH group of the indole ring is essential for this transformation (entry 12).

Table 2. Substrate scope for the synthesis of CF_3-tryptamines[a]



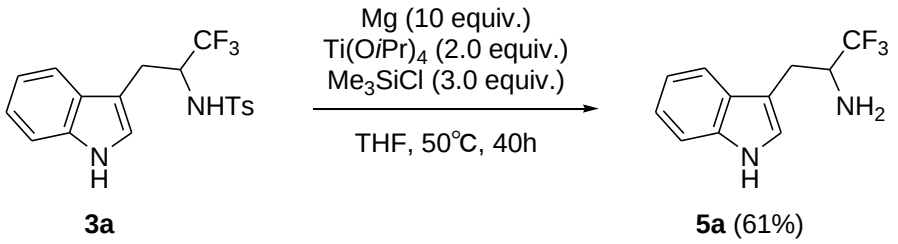
1 **2** **3**

entry	**2**	R	temp. (℃)	time (h)	**3**	yield[b] (%)
1	**2a**	H	100	17	**3a**	99
2	**2b**	5-OMe	100	15	**3b**	98
3	**2c**	5-OBn	100	19	**3c**	99
4	**2d**	5-Br	100	14	**3d**	99
5[c]	**2e**	5-COOMe	130	12	**3e**	94
6[d]	**2f**	5-CN	130	54	**3f**	76 (94)
7[e]	**2g**	4-OMe	100	20	**3g**	99
8	**2h**	4-OTBDMS	100	7	**3h**	99
9	**2i**	4-OH	100	24	**3i**	NR[f]
10	**2j**	2-Ph	100	10	**3j**	97
11	**2k**	2-Me	100	11	**3k**	99
12	**2l**	1-Me	100	24	**3l**	NR[f]

[a] The reaction of **1** (1.0 equiv.) with indoles **2** (1.3 equiv.) was carried out. [b] Isolated yield. [c] The reaction of **1** (1.0 equiv.) with indole **2e** (2.3 equiv.) was conducted in the presence of Et_2Zn (2.3 equiv.) in chlorobenzene. [d] The reaction of **1** (1.0 equiv.) with indole **2f** (2.3 equiv.) was conducted in the presence of Et_2Zn (2.3 equiv.) in chlorobenzene/THF = 10/1. [e] The reaction was conducted in chlorobenzene at 100 ℃. [f] No reaction.

Finally, deprotection of the NH-Ts group to give free NH_2 was examined. This deprotection often encountered the difficulty. The author referred to the procedure

reported by Okamoto et al.. Thus the adduct **3a** was exposed to reductive cleavage conditions.[12] Although the reaction was sluggish, the corresponding free NH_2-CF_3-tryptamine **5a** was obtained in 61 % yield (Scheme 2).



3a **5a** (61%)

Scheme 2. Deprotection of **3a** to give **5a**

5.3. Conclusion

In conclusion, the author has developed the synthesis of CF_3-tryptamine from **1** and indoles using diethylzinc (Et_2Zn) as a base with excellent yields and complete regioselectivity. It is noteworthy that this reaction has its simplicity, practicality, and broad functional group tolerance. Further efforts to transform the adducts into analogous biologically active molecules are underway in our laboratory.

5.4. Experimental

5.4.1. General information

^1H, ^{13}C, and ^{19}F NMR spectra were measured in $CDCl_3$ and/or DMSO-d_6 solutions,

unless otherwise stated. Chemical shifts were given by δ relative to that of an internal Me_4Si (TMS) for ^1H NMR and ^{13}C NMR spectra. On the other hand, chemical shifts were given by δ relative to that of $CFCl_3$ for ^{19}F NMR spectra using an internal $CF_3C_6H_5$ (benzotrifluoride) or C_6F_6. Infrared (IR) spectra are reported in cm^{-1}. Melting points are uncorrected.

5.4.2. Preparation of 3a

A 25 mL two-neck flask equipped with a magnetic stir bar, a stopcock and, a three-way stopcock was charged with **1** mL of toluene under argon. To this solution was successively added indole **2a** (34.4 mg, 0.294 mmol, 1.3 equiv.), 2-CF_3-*N*-Ts-aziridine **1** (60.0 mg, 0.226 mmol, 1.0 equiv.), and Et_2Zn (1.06 M in hexane solution, 0.28 μL, 1.3 equiv.). After the mixture was stirred for 5 min at room temperature, the flask was immersed in a preheated (100 °C) oil bath and stirred at this temperature for 17 h until the complete consumption of **1** (checked by TLC and GC-MS). After the reaction mixture was cooled to room temperature, to the mixture was added a saturated aqueous solution of NH_4Cl (3 mL), and the resulting mixture was extracted with EtOAc (2 mL) three times. The combined organic fractions were dried over sodium sulfate. To this solution was added a spoonful of silica gel, and the resulting suspension was carefully concentrated in vacuo. The residue was purified by chromatography on a silica gel column (hexane/EtOAc = 20/1 then 1/1 as an eluent) to give **3a** (85.9 mg, 99 %) as a pale pink solid.

5.4.2. Preparation of 5a[3c]

A 25 mL two-neck flask equipped with a magnetic stir bar, a stopcock and a three-way

stopcock was charged with Mg turnings (62.3 mg, 2.56 mmol, 10.0 equiv). This flask was heated by a heat-gun under vacuo for 15 min. After the flask was cooled to room temperature, to the flask was successively added THF (2 mL), Me_3SiCl (0.1 mL, 0.788 mmol, 3.0 equiv.), $Ti(O\textit{i}Pr)_4$ (0.15 mL, 0.507 mmol, 2.0 equiv.), and **3a** (101.3 mg, 0.265 mmol, 1.0 equiv.) under argon. The mixture was stirred at 50 °C for 40 h. After cooling to room temperature, to the mixture was successively added an aqueous 2M-NaOH solution (0.2 mL), ether (10 mL), Celite (0.5 g), and NaF (0.5 g). After the resulting suspension was stirred for 1 h, the mixture was filtered through a pad of Celite. The pad of Celite was washed with ether (10 mL) and to the combined filtrate was added an aqueous 2M-NaOH solution (5 mL). After the mixture was stirred for 1 h, the organic layer was separated. The aqueous layer was extracted with ether (5 mL x 3), and the combined organic fractions were dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by chromatography on a silica gel column NH (Chromatorex, Fuji Silysia, hexane/AcOEt = 1/1) to give the desired product **5a** as a white solid (36.7 mg, 61 %).

5.4.3. Characteristic spectroscopic data of products (3a-3h, 3j and 3k, 5a)

N-[3-(1H-indol-3-yl)-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3a)

Pink solid; yield 99 %; mp: 170.3–170.5 °C; IR (KBr) 3410, 3273, 2930, 1599, 1458, 1270, 1175, 1120, 949, 805, 666, 576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (s, 1H), 7.43–7.38 (m, 3H), 7.31–7.26 (m, 1H), 7.22–7.16 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.01–6.98 (m, 3H), 4.88 (d, *J* = 8.6 Hz, 1H), 4.29–4.18 (m, 1H), 3.26 (dd, *J* = 15.0, 3.9 Hz, 1H), 2.97 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6 = 4/1, 101 MHz) δ 140.9, 136.7, 135.3, 127.5, 125.5, 124.6, 124.1 (q, *J* = 283.2 Hz),

123.3, 119.9, 117.5, 116.4, 110.4, 106.5, 54.3 (q, J = 29.0 Hz), 23.2, 20.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.3 (d, J = 6.4 Hz); GC-MS (EI, m/z, 70 eV) 382 (7, M^+), 226 (1), 211 (3), 130 (100), 103 (4), 91 (8), 77 (5), 65 (3), 51 (1); Anal. Calcd. for $C_{18}H_{17}F_3N_2O_2S$: C, 56.54; H, 4.48; N, 7.33. Found: C, 56.54; H, 4.57; N, 7.24.

N-[3-{5-methoxy-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3b)

White solid; yield 98 %; mp: 172.5–173.5 °C; IR (KBr) 3414, 3396, 3290, 2975, 2929, 1587, 1333, 1262, 1172, 1113, 1027, 946, 797, 563, 545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.4 Hz, 2H), 6.99 (s, 1H), 6.90 (s, 1H), 6.86 (d, J = 8.6 Hz, 1H), 4.85 (d, J = 8.6 Hz, 1H), 4.27–4.12 (m, 1H), 3.86 (s, 3H), 3.25 (dd, J = 14.9, 3.9 Hz, 1H), 2.98 (dd, J = 14.9, 7.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 4/1, 101 MHz) δ 153.5, 142.5, 136.9, 131.5, 128.6, 126.9, 125.7, 124.7 (q, J = 282.7 Hz), 124.6, 111.9, 111.4, 107.4, 99.7, 55.7, 55.3 (q, J = 29.4 Hz), 24.4, 21.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –75.9 (d, J = 7.1 Hz); GC-MS (EI, m/z, 70 eV) 412 (9, M^+), 241 (2), 160 (100), 145 (10), 117 (6), 91 (8), 65 (2); Anal. Calcd. for $C_{19}H_{19}F_3N_2O_3S$: C, 55.33; H, 4.64; N, 6.79. Found: C, 55.09; H, 4.72; N, 6.75.

N-[3-{5-benzyloxy-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3c)

Pale pink solid; yield 99 %; mp: 139.9–140.5 °C; IR (KBr) 3430, 3405, 3257, 2922, 2875, 1585, 1486, 1456, 1334, 1272, 1173, 1120, 1092, 1057, 944, 845, 742, 671, 570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.44–7.30

(m, 5H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.97–6.90 (m, 5H), 5.11 (s, 2H), 4.94 (d, *J* = 8.8 Hz, 1H), 4.19–4.05 (m, 1H), 3.21 (dd, *J* = 15.1, 4.3 Hz, 1H), 2.91 (dd, *J* = 15.1, 8.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.1, 143.1, 137.5, 136.2, 131.4, 129.0, 128.5, 127.9, 127.6, 127.0, 126.2, 124.7, 124.7 (q, *J* = 282.6 Hz), 112.9, 112.0, 107.3, 101.6, 70.9, 55.0 (q, *J* = 29.5 Hz), 24.7, 21.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.1 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/*z*, 70 eV) 488 (24, M^+), 397 (1), 333 (3), 241 (98), 236 (95), 225 (4), 214 (7), 172 (5), 145 (38), 117 (24), 91 (100), 65 (12); Anal. Calcd. for $C_{25}H_{23}F_3N_2O_3S$: C, 61.46; H, 4.75; N, 5.73. Found: C, 61.38; H, 4.82; N, 5.70.

N-[3-{5-bromo-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3d)

White solid; yield 99 %; mp: 140.7–141.7 °C; IR (KBr) 3405, 3279, 2923, 1598, 1462, 1429, 1331, 1270, 1177, 1161, 1092, 948, 795, 668, 576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H), 7.50–7.40 (m, 3H), 7.29–7.24 (m, 1H), 7.19–7.14 (m, 1H), 7.07–7.03 (m, 3H), 4.86–4.73 (m, 1H), 4.22–4.09 (m, 1H), 3.19 (d, *J* = 15.1, 4.1 Hz, 1H), 2.95–2.87 (m, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD = 4/1, 101 MHz) δ 143.4, 136.0, 134.8, 129.2, 128.4, 126.3, 125.4, 124.8, 124.6 (q, *J* = 282.6 Hz), 120.4, 112.84, 112.82, 107.3, 55.0 (q, *J* = 30.3 Hz), 24.5, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.3 (d, *J* = 5.3 Hz); GC-MS (EI, *m*/*z*, 70 eV) 462 (8, $M^+[^{81}Br]$), 460 (8 ,$M^+[^{79}Br]$), 291 (3), 289 (3), 210 (96), 208 (100), 154 (5), 129 (29), 102 (8), 91 (19), 65 (5); HRMS (FAB, *m*/*z*) Calcd. for $C_{18}H_{16}BrF_3N_2O_2S$: 460.0068; Found: 460.0070.

N-[3-{5-methoxycarbonyl-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3e)

White solid; yield 94 %; mp: 146.0–146.7 °C; IR (KBr) 3292, 2958, 1694, 1620, 1437, 1364, 1269, 1174, 943, 773, 701, 576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 8.16 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.12 (s, 1H), 6.93 (d, *J* = 7.9 Hz, 2H), 5.23 (d, *J* = 7.7 Hz, 1H), 4.28–4.11 (m, 1H), 3.96 (s, 3H), 3.27 (dd, *J* = 15.0, 3.7 Hz, 1H), 2.94 (dd, *J* = 15.0, 9.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 4/1, 101 MHz) δ 168.6, 142.4, 138.8, 137.0, 128.5, 126.2, 125.5, 125.3, 124.6 (q, *J* = 282.6 Hz), 122.5, 120.6, 120.4, 110.9, 109.3, 55.7 (q, *J* = 30.4 Hz), 51.6, 23.9, 20.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.6 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/z, 70 eV) 440 (6, M^+), 409 (3), 269 (3), 188 (100), 156 (3), 129 (12), 91 (9); Anal. Calcd. for $C_{20}H_{19}F_3N_2O_4S$: C, 54.54; H, 4.35; N, 6.36. Found: C, 54.70; H, 4.27; N, 6.35.

N-[3-{5-cyano-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3f)

White solid; yield 76 %; mp: 181.0–183.0 °C; IR (KBr) 3261, 2923, 2224, 1736, 1620, 1471, 1330, 1272, 1177, 1126, 947, 808, 675, 571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (s, 1H), 7.72 (s, 1H), 7.53 (d, *J* = 6.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.14 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 9.4 Hz, 1H), 4.28–4.17 (m, 1H), 3.25 (d, *J* = 15.1, 4.3 Hz, 1H), 3.01 (d, *J* = 15.1, 8.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 4/1, 101 MHz) δ 142.6, 137.9, 137.3, 128.8, 126.6, 126.2, 125.7, 124.6 (q, *J* = 282.6 Hz), 124.0, 123.5, 120.7, 112.1, 109.0, 101.2, 55.7 (q, *J* = 30.3 Hz), 24.1, 21.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.5 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/z, 70 eV) 407 (8, M^+), 236 (5), 155 (100), 128 (3), 91 (10), 65 (3); HRMS (FAB, *m/z*) Calcd. for $C_{19}H_{16}F_3N_3O_2S$: 407.0915; Found: 407.0901.

N-[3-{4-methoxy-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3g)

White solid; yield 99 %; mp: 69.5–70.9 °C; IR (KBr) 3407, 3277, 2936, 1590, 1509, 1340, 1272, 1174, 1126, 1090, 946, 810, 734, 668, 571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.82–6.72 (m, 3H), 6.45 (d, *J* = 7.9 Hz, 1H), 6.05 (d, *J* = 6.7 Hz, 1H), 4.15–3.99 (m, 1H), 3.96 (s, 3H), 3.22 (dd, *J* = 14.1, 2.6 Hz, 1H), 3.06–2.97 (m 1H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.0, 142.4, 137.9, 136.1, 128.5, 125.6, 124.8 (q, *J* = 282.6 Hz), 122.8, 122.5, 116.9, 108.4, 105.2, 99.8, 55.4 (q, *J* = 29.6 Hz), 55.2, 25.0, 21.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –77.5 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/*z*, 70 eV) 412 (18, M^+), 241 (2), 160 (100), 130 (21), 117 (5), 91 (10), 65 (3); HRMS (FAB, *m/z*) Calcd. for $C_{19}H_{19}F_3N_2O_3S$: 412.1068; Found: 412.1068.

N-[3-{4-tert-butyldimethylsilyloxy-(1H-indol-3-yl)}-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3h)

White solid; yield 99 %; mp: 65.0–67.0 °C; IR (KBr) 3400, 3257, 2932, 2860, 1580, 1504, 1340, 1174, 943, 862, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.26 (d, *J* = 6.4 Hz, 1H), 4.00–3.89 (m, 1H), 3.23–3.10 (m, 2H), 2.24 (s, 3H), 1.03 (s, 9H), 0.396 (s, 3H), 0.356 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 148.7, 142.2, 138.4, 136.1, 128.5, 125.4, 124.8 (q, *J* = 282.6 Hz), 122.5, 122.3, 118.9, 108.6, 108.1, 105.4, 58.1 (q, *J* = 29.6 Hz), 26.2, 24.2, 21.3, 18.9, –3.34, –3.86; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –77.0 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/*z*, 70 eV) 512 (28, M^+), 455 (100), 300 (32), 260 (55), 222 (36), 188 (19), 91 (26), 73

(16); Anal. Calcd. for $C_{24}H_{31}F_3N_2O_3SSi$: C, 56.23; H, 6.09; N, 5.46. Found: C, 55.95; H, 6.14; N, 5.45.

N-[3-(2-phenyl-1H-indol-3-yl)-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3j)

White solid; yield 97 %; mp: 180.0–181.5 °C; IR (KBr) 3415, 3274, 3056, 1598, 1491, 1325, 1296, 1181, 1156, 1124, 955, 740, 665, 571, 547 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 7.55–7.40 (m, 4H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.27–7.13 (m, 5H), 6.86 (d, *J* = 8.0 Hz, 2H), 4.37 (d, *J* = 8.6 Hz, 1H), 4.23–4.11 (m, 1H), 3.37 (dd, *J* = 14.9, 3.7 Hz, 1H), 3.08 (dd, *J* = 14.9, 10.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 4/1, 101 MHz) δ 142.3, 136.9, 135.8, 135.7, 132.5, 128.5, 128.1, 127.8, 127.6, 125.3, 124.6 (q, *J* = 282.7 Hz), 121.6, 119.2, 117.6, 110.91, 110.86, 104.8, 55.4 (q, *J* = 30.0 Hz), 23.7, 20.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –77.2 (d, *J* = 6.0 Hz); GC-MS (EI, *m/z*, 70 eV) 458 (2, M^+), 302 (1), 206 (100), 178 (8), 155 (2), 128 (2), 91 (5); HRMS (FAB, *m/z*) Calcd. for $C_{24}H_{21}F_3N_2O_2S$: 458.1276; Found: 458.1294.

N-[3-(2-methyl-1H-indol-3-yl)-1,1,1-trifluoropropan-2-yl]-4-methylbenzenesulfonamide (3k)

White solid; yield 99 %; mp: 177.5–178.0 °C; IR (KBr) 3416, 3272, 2921, 1596, 1464, 1330, 1246, 1178, 1126, 956, 805, 746, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 1H), 7.36–7.29 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.14–7.03 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 4.80 (d, *J* = 9.0 Hz, 1H), 4.22–4.08 (m, 1H), 3.18 (dd, *J* = 15.0, 4.5 Hz, 1H), 2.91 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 4/1, 101 MHz) δ 142.5, 137.1, 135.2, 132.9, 128.7, 127.8, 125.6, 124.7 (q, *J* = 283.3

Hz), 120.5, 118.8, 116.6, 110.2, 103.8, 55.5 (q, *J* = 28.8 Hz), 23.8, 21.0, 10.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ –76.6 (d, *J* = 6.8 Hz); GC-MS (EI, *m*/*z*, 70 eV) 396 (7, M^+), 144 (100), 115 (3), 91 (7), 77 (2), 65 (2); Anal. Calcd. for $C_{19}H_{19}F_3N_2O_2S$: C, 57.57; H, 4.83; N, 7.07. Found: C, 57.33; H, 4.81; N, 7.05.

3-(1H-indol-3-yl)-1,1,1-trifluoropropan-2-amine (5a)[3c]

White solid; yield 61 %; mp: 72.0–72.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.26–7.20 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 3.67–3.53 (m, 1H), 3.28 (dd, *J* = 14.5, 3.1 Hz, 1H), 2.82 (dd, *J* = 14.5, 10.2 Hz, 1H), 1.35 (bs, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.4, 127.1, 126.6 (q, *J* = 280.8 Hz), 123.2, 122.3, 120.0, 118.5, 111.3, 110.5, 53.5 (q, *J* = 28.1 Hz), 26.1 (q, *J* = 1.8 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ –79.5 (d. *J* = 8.1 Hz); GC-MS (EI, *m*/*z*, 70 eV) 228 (16, M^+), 158 (1), 130 (100), 103 (6), 77 (8).

5.4.4. Crystal Data for 3a

($C_{18}H_{17}F_3N_2O_2S$): *M* = 382.40, *T* = 113 K, triclinic, space group P-1, *a* = 9.074(2) Å, *b* = 9.836(2) Å, *c* = 11.599(3) Å, α = 70.045(12)˚, β = 68.705(11)˚, γ = 72.73(2)˚, *V* = 888.9(3) Å^3, *Z* = 2, *Dcalc* = 1.429 Mg m^{-3}, μ = 0.227 mm^{-1}, λ = 0.71075 Å, θ_{max} = 27.50°, 16726 measured reflection, 4053 independent reflections, 239 refined parameters, GOF = 1.070, $R[F^2 > 2\sigma(F^2)]$ = 0.0339, $wR(F^2)$ = 0.0999. The intensity data were collected on a Rigaku Saturn724 diffractometer using multi-layer mirror monochromated Mo-Kα. The structure was solved by direct methods (SIR2008[1]) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL97[2]). Hydrogen atoms were refined using

the riding model. CCDC-990028 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_ request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting. The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

5.5. References

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(11) CCDC-990028 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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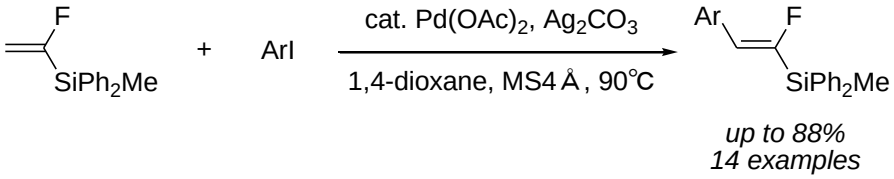
Chapter six

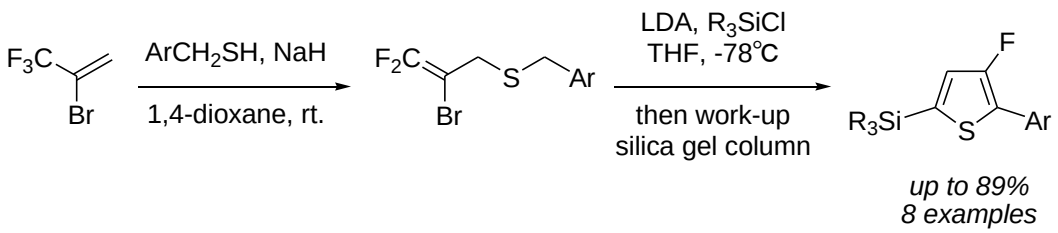
Overall Conclusions

In conclusion, four new strategies for synthesis of fluorinated compounds are reported. Mizoroki-Heck reaction of (1-fluorovinyl)methyldiphenylsilane with various aryl iodides in good to high yields with excellent stereoselectivity. The addition of Ag_2CO_3 and MS4Å is effective in this reaction (Scheme 1).



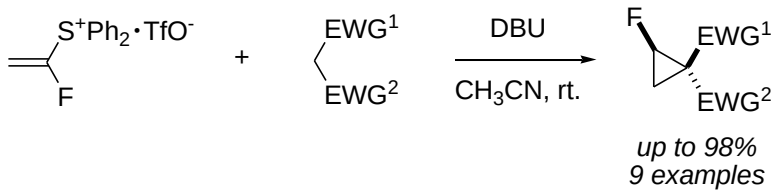
Scheme 1. Mizoroki-Heck reaction of (1-fluorovinyl)methyldiphenylsilane

The thiolate generated from thiol and sodium hydride in 1,4-dioxane reacted with 2-bromo-3,3,3-trifluoro-1-propene at room temperature to afford the corresponding 2-bromo-3,3-difluoroallyl sulphide as S_N2' product. The generated corresponding product using benzyl thiol was treated by silyl chloride and LDA, through work-up and silica gel column produced 2-aryl-3-fluoro-5-silylthiophenes (Scheme 2).



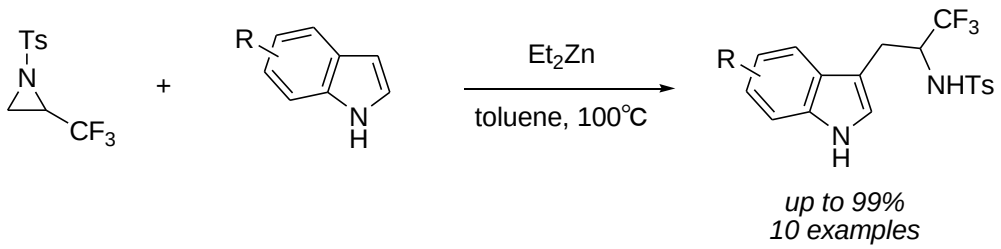
Scheme 2. Synthesis of 2-aryl-3-fluoro-5-silylthiophenes

The access to functionalized mono-fluorinated cyclopropanes and aziridines using (1-fluorovinyl)diphenylsulfonium salt was accomplished (Scheme 3).



Scheme 3. Synthesis of mono-fluorinated cyclopropanes

Diethylzinc-promoted synthesis of CF_3-containing tryptamine analogues from indoles and 2-CF_3-*N*-Ts-aziridine was achieved. CF_3-containing tryptamines were prepared with perfect stereoselectivity and excellent yield in this reaction (Scheme 4).



Scheme 4. Synthesis of CF_3-containing tryptamines

The use of our new methods enables to synthesize some new partially fluorinated compounds. These compounds may be useful candidates for bioactive molecules and/or functional materials.

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